SYNTHESIS OF 2-IMINO-2-OXO-1,3,2-OXAZAPHOSPHORINANES

BY

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This thesis, written by Nidal Y. Abu-Thabit under the direction of his thesis advisor and approved by his thesis committee, has been presented to and accepted by Dean of Graduate Studies, in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE IN CHEMISTRY.

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All praise and glory be to Allah for his limitless help and guidance. Peace pleasing of Allah be upon his prophet Mohammed.

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THESIS ABSTRACT

Name: Nidal Y. M. Abu-Thabit.

Title: Synthesis of 2-imino-2-oxo-1,3,2-oxazaphosphorinanes.

Major Field: Chemistry

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The thesis outlines the development of suitable methodology in order to prepare 2-imino-1,3,2-oxazaphosphorinanes. α-Methylbenzylamines were converted to the corresponding of 2-amino-2-oxo-1,3,2-oxazaphosphorinanes with good overall yields. X-ray structures were obtained for both (2*R*)-chloro-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane and racemic 2-(*R*)-amino-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane. This conformational study clearly indicated that the *exo* cyclic P=O is equatorial whereas the chlorine and amino groups are axial.

Aldimines were obtained upon heating the 2-amino-2-oxo-1,3,2-oxazaphosphorinanes under reflux in dichloromethane for 24 hours with two equivalents of 4-substituted benzaldehyde derivatives and five equivalents of titanium (IV) ethoxide. However, five equivalents of acetophenone and ten equivalents of titanium (IV) ethoxide and heating under reflux in toluene were necessary for the synthesis of the corresponding ketimine derivative. This novel class of activated imine underwent a diastereoselective 1,4-addition reaction with diethylaluminium cyanide (48% de). The major addition product was obtained in a diastereomerically pure form upon recrystallization from ethyl acetate and hexane.

ملخص الرسالة

الاســـــــــــم: نضـــال يوســف محـــمد أبو ثابـــت.

عنوان الرسالة: تصنيـــع مركبـــات (2-imino-1,3,2-oxazaphosphorinanes).

التخصـــــــص: الكيـــميـــاء

تاريخ التخـرج: مـــايـو / 2005

ان الاطروحة تتناول تطوير طريقة مناسبة لتحضير مركبات (2-imino-1,3,2-oxazaphosphorinanes). تم تحويل α-Methylbenzylamines الى 2-imino-1,3,2-oxazaphosphorinanes بنسب جيدة. تم الحصول على الشكل البنلئي بواسطة الاشعة السينية للمركبات (2*R*)-chloro-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane and racemic 2-(*R*)-amino-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane. لقدأوضحت هده الدراسة للشكل التركيبي ان الرابطه المضاعفة بين الأكسجين خارج الحلقة و الفسفور تكون في وضع مائل (equatorial) بينما تكون مجموعتا الأمين و الكلور في وضع عامودي (axial).

تم الحصول على الألدأمين بتسخين 2-imino-1,3,2-oxazaphosphorinanes لمدة 24 ساعة في ثنائي كلوريد الميثيل باستخدام مكافئين من مشتقات البنزالديهايد مع خمس مكافئات من التيتانيوم الأيثيلي (IV). بينما كان من الضروري استخدام خمس مكافئات من الأسيتوفينون و عشر مكافئلت من التيتانيوم الأيثيلي (IV) وبالتسخين ل 24 ساعه في التوليوين لتحضير مشتقة الكيتامين. تمت اضافة الديايثيل الومينيوم سيانيد لهدا النوع الفريد من مشتقات الأيمينات بشكل غير متماثل (48% d.e) . وتم فصل المتماثل الرئيسي بشكل نقي بواسطة الترسيب من محلول اليثيل أسيتات و الهكسان

CHAPTER 1

1. INTRODUCTION

1.1 Literature Review

There is an ever increasing demand for enantiomerically pure compounds, especially from the pharmaceutical industry, which must comply with stricter regulations imposed by the authorities. The world-wide sale of single enantiomer drugs in 2001 amounts to $147 billion, or approximately 36% of the total market of pharmaceutical products.[1] To meet this demand asymmetric synthesis, the stereoselective synthesis of enantiopure materials, has rapidly developed into one of the most important fields of chemical research.

Stereoselective synthesis can be performed in three different ways. The first is under substrate control using chiral auxiliaries, the second is under reagent control and the third utilizes chiral catalysts. This thesis will outline the novel utilization of the oxazaphosphorinane chiral auxiliary.

1.1.1 Oxazaphosphorinanes

The 2-oxo-1,3,2-oxazaphosphorinane ring system is found in many biologically active molecules. Several cancer drugs such as cyclophosphamide **(1a)**, isophosphamide **(1b)** and triphosphamide **(1c)** contain this ring system (Figure 1).[2]

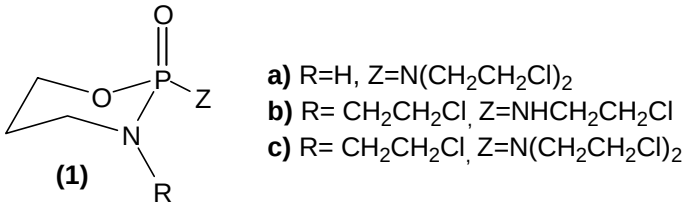
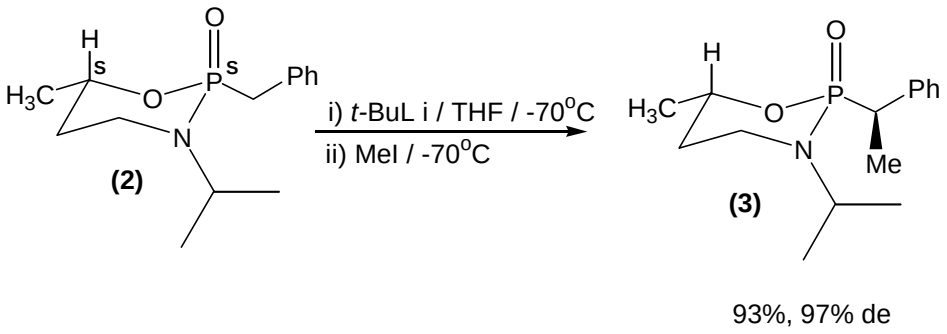


Figure 1

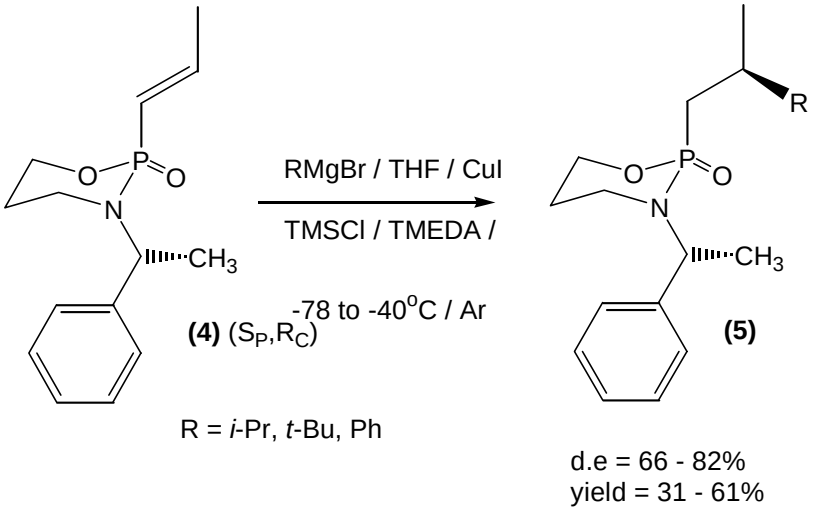
Recently, several research groups have utilized 2-oxo-1,3,2-oxazaphosphorinanes **(1)**, which contain a bulky *N*-substituent, as a novel class of chiral auxiliaries and as such has led to new methods in asymmetric synthesis. Denmark prepared a series of racemic and enantiomerically pure 2-oxo-1,3,2 oxazaphosphorinanes. The diastereoselectivity of alkylation of the derived anions was examined as a function of ring substitution.[3] In a later study the diastereoselectivity of the alkylations was found to be sensitive to the size of the *N*-substituents.



Scheme 1

The highest diastereoselectivity was obtained with 2-benzyl-6-methyl-2-oxo-1,3,2-oxazaphosphorinane (**2**), which contained a *N*-isopropyl substituent (Scheme 1).[4] These stereoselective alkylation reactions were subsequently utilized for the highly

enantioselective synthesis of both α-alkylphosphonates[4,5] and α-alkoxyphosphonates.[5] The same group also reported that racemic 2-allyl-1,3,2-oxazaphosphorinanes-2-oxides underwent extremely diastereoselective Michael additions to cyclic enones.[6] Evans reported the enantioselective aldol reactions of a chiral 2-oxo-2-propionyl-1,3,2-oxazaphosphorinane.[7]



Scheme 2

In the last few years Afarinkia and co-workers have made further advances in this field of asymmetric synthesis. They reported the first examples of diastereoselective additions of carbon nucleophiles to 2-(prop-2-enyl)-2-oxo-1,3,2-oxazaphosphorinanes.[8-10] Subsequently, the same group reported diastereoselective additions of carbon nucleophiles to enantiopure 2-(prop-2-enyl)-2-oxo-1,3,2-oxazaphosphorinanes (**4**) (Scheme 2).[11] The major addition product (**5**) was obtained as a single diastereomer following recrystallization from petroleum ether. Afarinkia also recently reported that *N*-substituted 2-oxo-2-propyl-1,3,2-oxazaphosphorinanes undergo diastereoselective alkylations.[12,13] A

review of this group's work on asymmetric induction utilizing such chiral oxazaphosphorinane auxiliaries has recently been published.[14]

1.1.2 Additions to Activated Imines

The enantioselective addition of carbon nucleophiles to imines[15,16] is a very important process due to the predominant role that chiral amines play in biologically important systems. Furthermore, chiral amines are also useful building blocks for the synthesis of various medicinal compounds such as rivastigmine (**6**), tamsulosin (**7**), indanorex (**8**) and repaglinide (**9**) (Figure 2).[17]

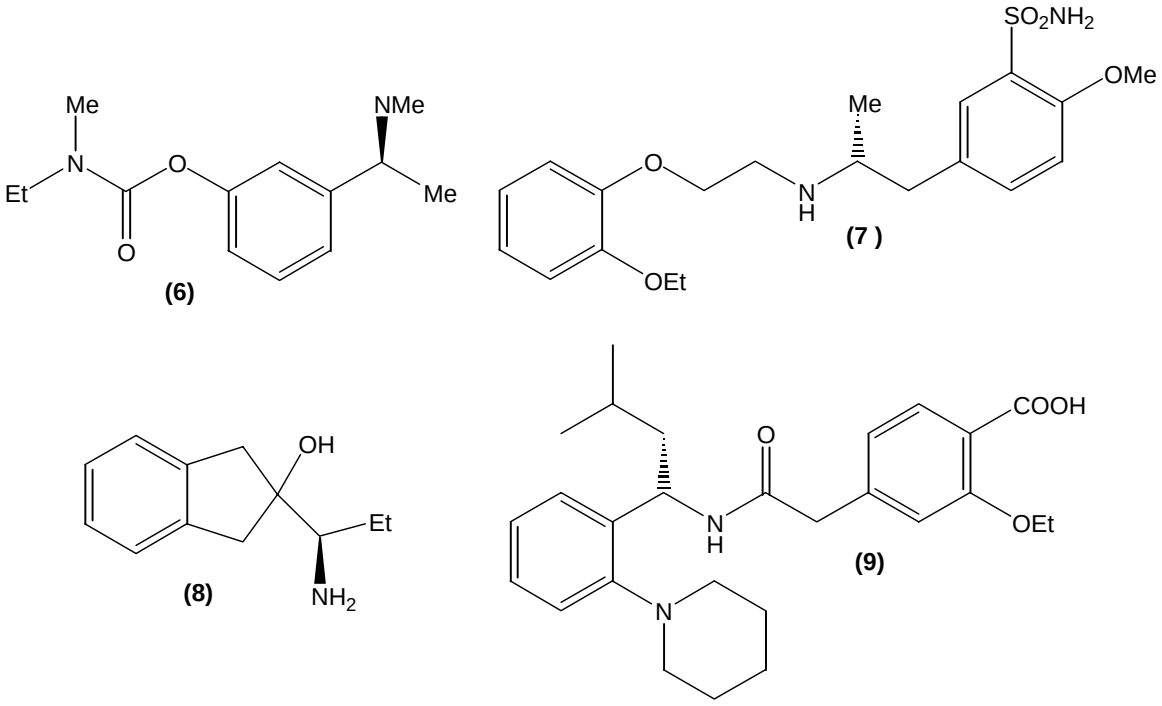


Figure 2

The chiral environment of the starting imine plays an important role for the success of the enantioselective additions. A variety of chiral auxiliaries have been utilized for nucleophilic addition to imines. These include imines derived from chiral amines (**10**-**13**), imines derived from chiral hydrazones (**14**-**16**), imines derived from chiral *N*-sulfinamines (**17**,**18**), imines derived from chiral oxime ethers (**19**) and imines derived from chiral nitrones (**20**) (Figure 3).

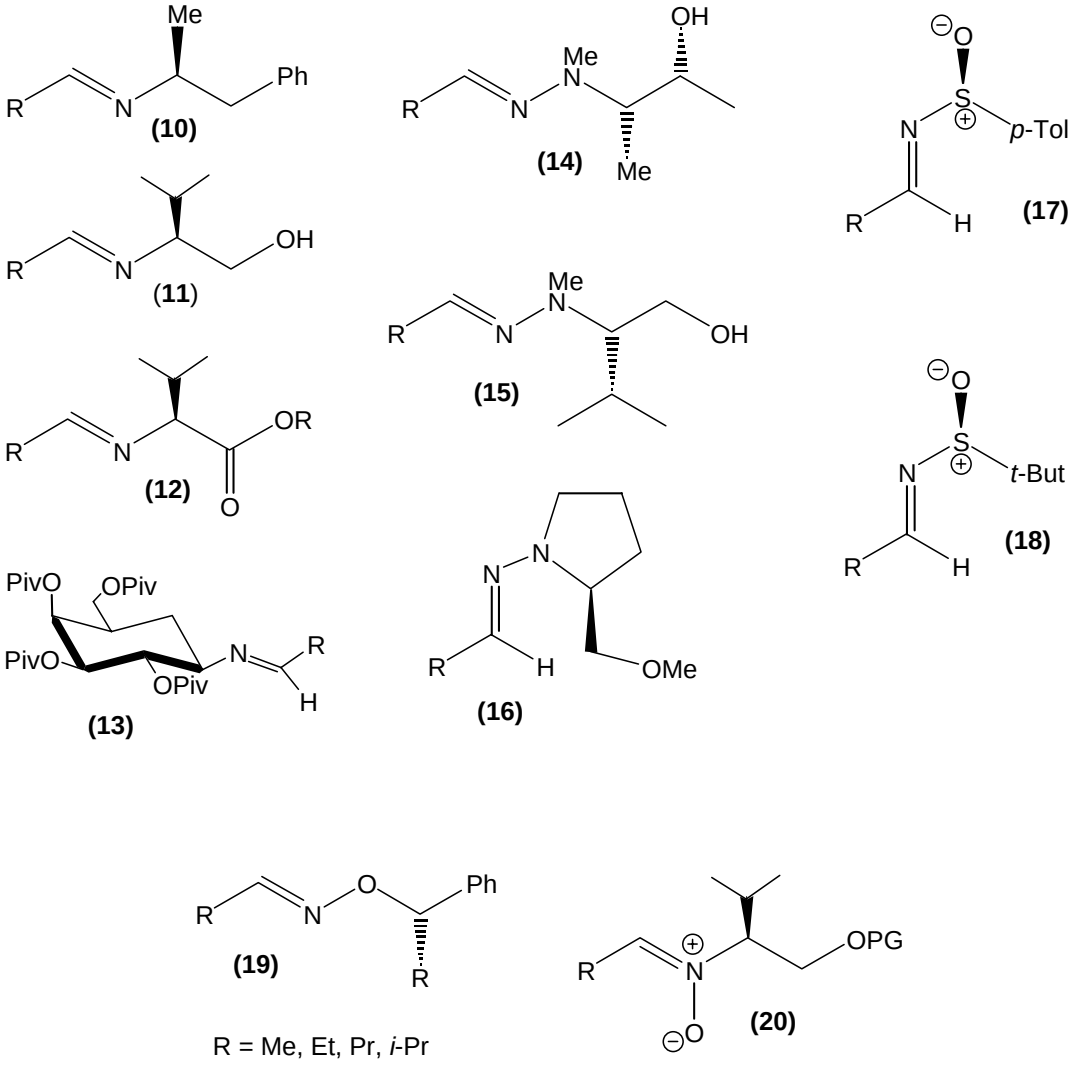
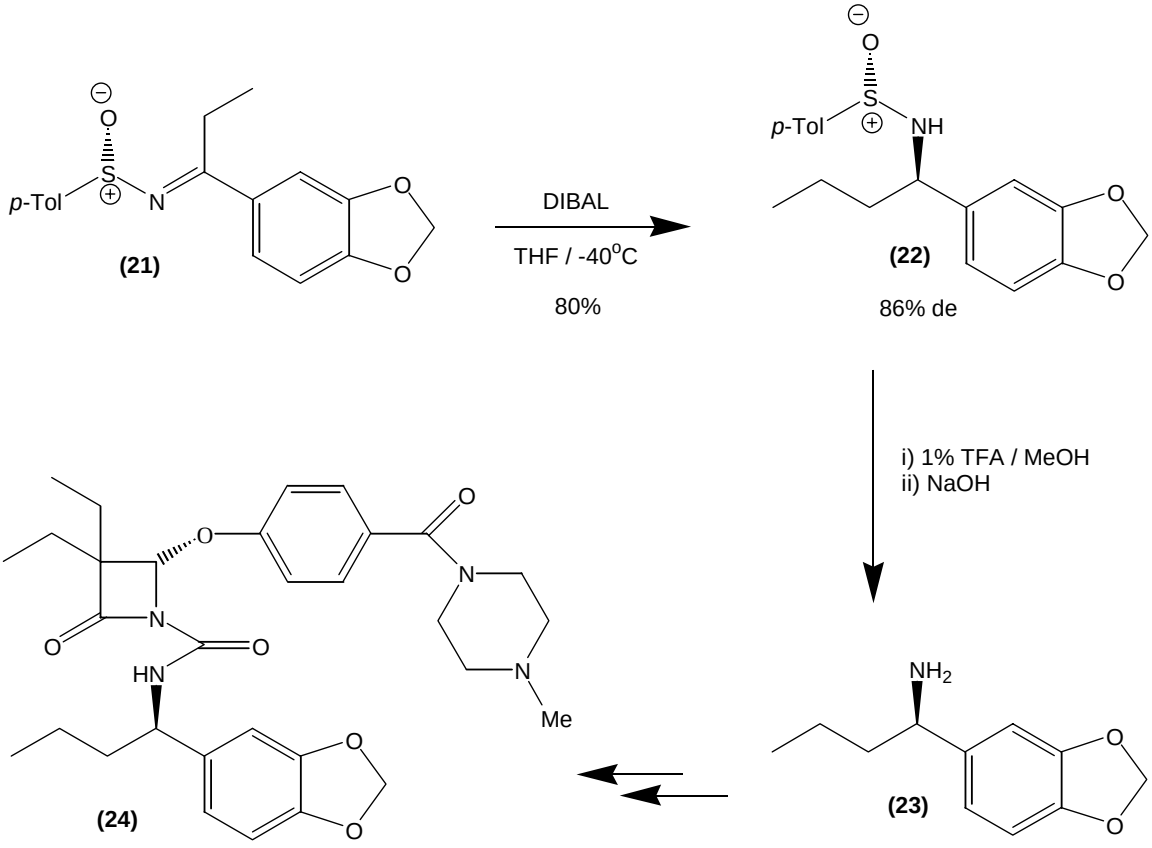


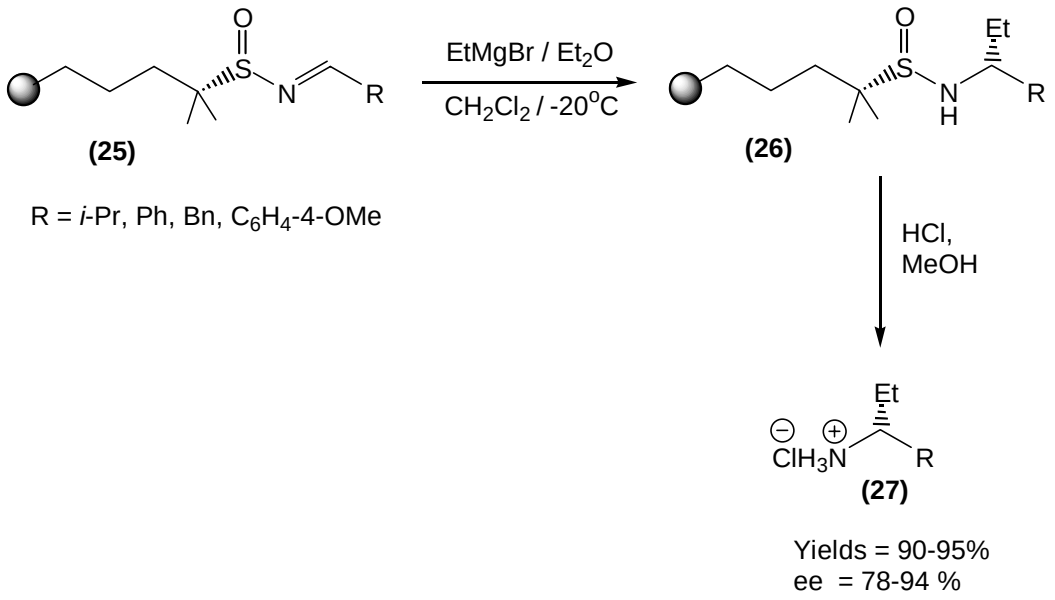
Figure 3

Sulfinimines (*N*-sulfinylimines) are an important class of activated imines that display unique reactivity and stereoselectivity due to the presence of the chiral *N*-sulfinyl group. Over the last ten years Davis has made major advances in asymmetric synthesis using *p*-toluenesulfinimines. He has completed the asymmetric synthesis of many natural products and bioactive molecules using this methodology. One example is the synthesis of human leukocyte elastase inhibitor, DMP 777, (**24**). [18] DIBAL-H reduction of the ketone-derived sulfinimine (**21**) afforded the corresponding sulfonamide (**22**) in 80% yield and 86% de. Removal of the sulfinyl group with TFA gave (**23**) which is a chiral amino unit found in (**24)** (Scheme 3).



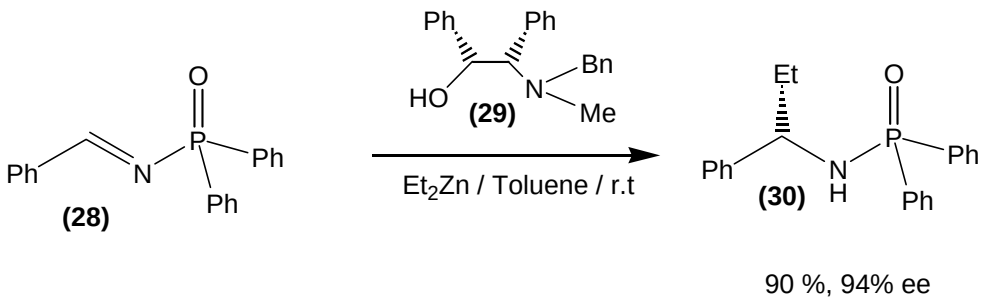
Scheme 3

Ellman recently developed an efficient synthesis of support-bound *tert*-butanesulfinimines (**25**) and demonstrated the utility of this linker for the asymmetric synthesis of enantioenriched amines (**27**) (Scheme 4).[19]



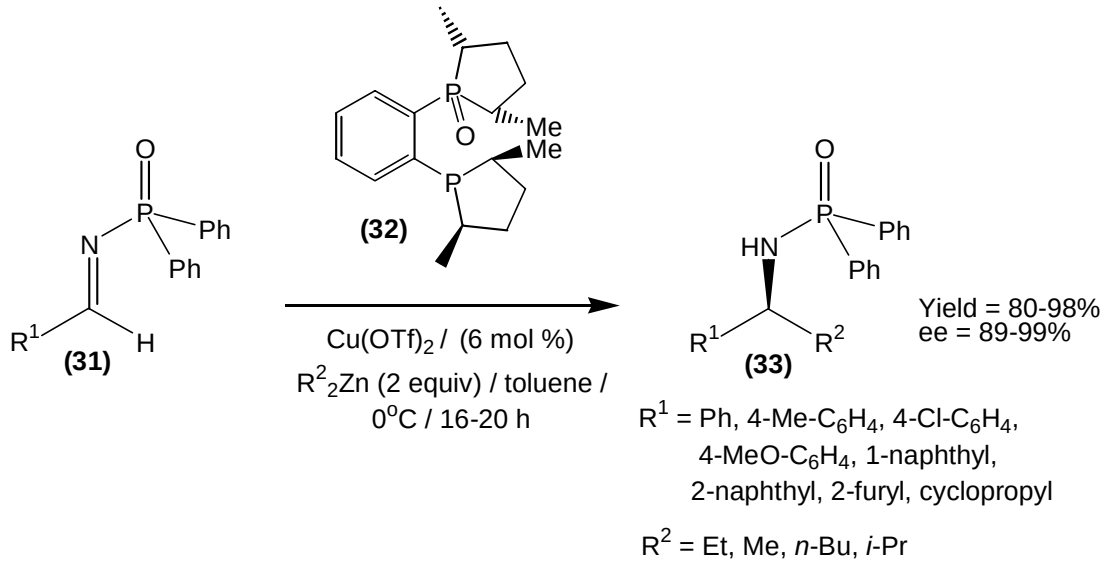
Scheme 4

Asymmetric 1,4-additions of carbon nucleophiles, especially diethyl zinc, to activated imines have been extensively studied.[20] Soai *et al* reported the enantioselective addition of diethylzinc to *N*-diphenylphosphinoylimines using chiral diimines, chiral diamines and chiral dendrimers as chiral ligands.[21] Another example of the use of chiral dendrimers as efficient chiral ligands for the enantioselective addition of diethylzinc to *N*-diphenylphosphinoylimines was recently reported.[22] Chiral amino alcohols (**29**) have also been utilized for the enantioselective addition of diethylzinc to *N*-diphenylphosphinoyl imines (**28**) (Scheme 5).[23,24] Enantiomerically enriched *N*-diphenylphosphinylamines (**30**) with excellent enantioselectivities (up to 94% ee) were obtained.



Scheme 5

Recently, Charette *et al*. have investigated the *bis*(phosphine) monoxide ligand (**32**) for the copper-catalyzed diorganozinc addition to *N*-phosphinoylimines (**31**). This required lower catalyst loading and the resulted phosphinoylamines (**33**) obtained in higher yields and enantiomeric excess (Scheme 6).[17,25] The same group reported the reaction mechanism in a recent paper. [26]



Scheme 6

1.2 Objectives and Work Plan

1.2.1 Objectives

The major objective of this work is to develop suitable methodology in order to prepare the 2-imino-1,3,2-oxazaphosphorinane (**34**). This novel class of activated imines are potential precursors to many biologically important building blocks such as α-aminophosphonic acids **(35)**, α-amino acids **(36)**, β-amino acids **(37)**, α-branched amines **(38)**, α,α-dibranched amines **(39)** and aziridines **(40)** (Figure 4).

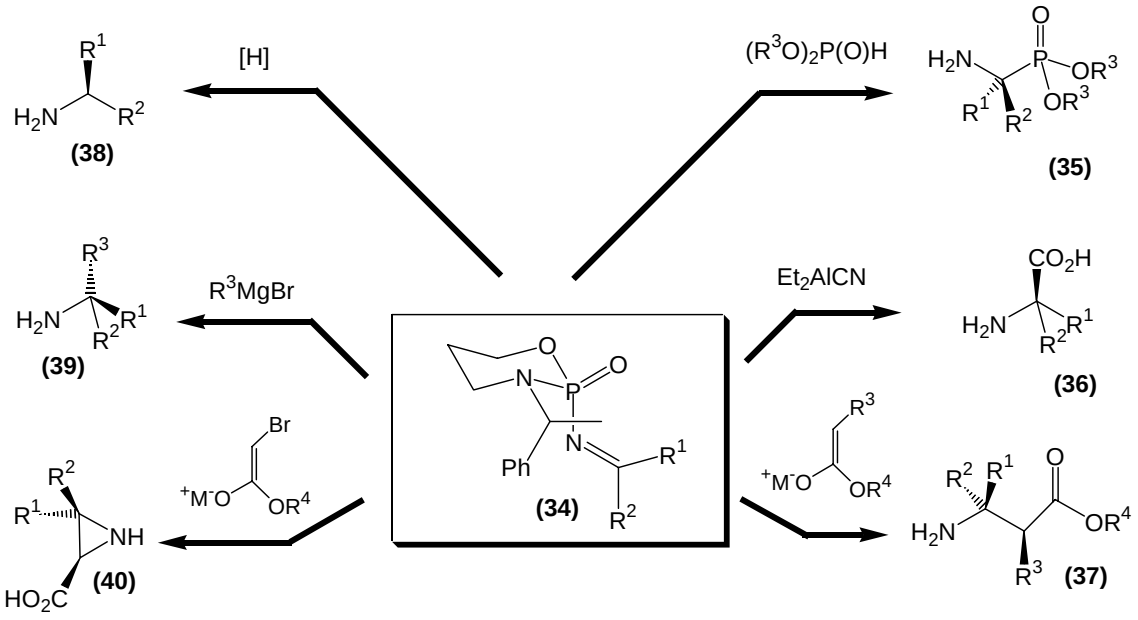


Figure 4

The chiral phosphorus auxiliary attached to the imine functional group has several important advantages. The electron withdrawing nature of the P=O moiety will increase the electrophilicity of the imine. This will enable the additions of nucleophiles to be

conducted at a lower temperature, with the potential of enhanced selectivity. Also, as this chiral auxiliary contains a phosphorus atom ^{31}P NMR can be utilized to follow the course of the addition reactions. Completion of the reaction is clearly indicated by the disappearance of the ^{31}P NMR of the starting imine. Also, ^{31}P NMR can act as a powerful tool to determine the stereochemical outcome of the addition reaction. Comparison of the integrals of the two ^{31}P NMR peaks, for the two diastereomeric addition products, is a simple yet precise method to determine the diastereoselectivity of this reaction.

1.2.2 Work Plan

This project primarily focuses upon the development of suitable methodology for the synthesis of 2-imino-2-oxo-1,3,2-oxazaphosphorinane **(34)**, a novel class of activated imine. The retrosynthetic pathway is outlined below (Figure 5). It is envisaged that imine **(34)** can be synthesized by the condensation of an aldehyde or ketone **(41)** and phosphorodiamidate **(42)**, which in turn can be synthesized from the corresponding phosphoramidochloridate **(43)**. This six membered oxazaphosphorinane ring system can be obtained from the cyclization of aminoalcohol **(44)**. This in turn can be obtained from aminoester **(45)**. Finally, this can be derived from α-methylbenzylamine **(46)** which is commercially available both in racemic and enantiomerically pure forms.

The aminoester **(45)**[27], amino alcohol **(44)**[28] and 2-chloro-2-oxo-1,3,2-oxazaphosphorinane **(43)**[29,30] have been previously reported in the literature. However, there are no reports of either the 2-amino-2-oxo-1,3,2-oxazaphosphorinane **(42)** and the

target 2-imino-2-oxo-1,3,2-oxazaphosphorinane **(34)**. Thus, they are novel compounds and so represent important synthetic targets.

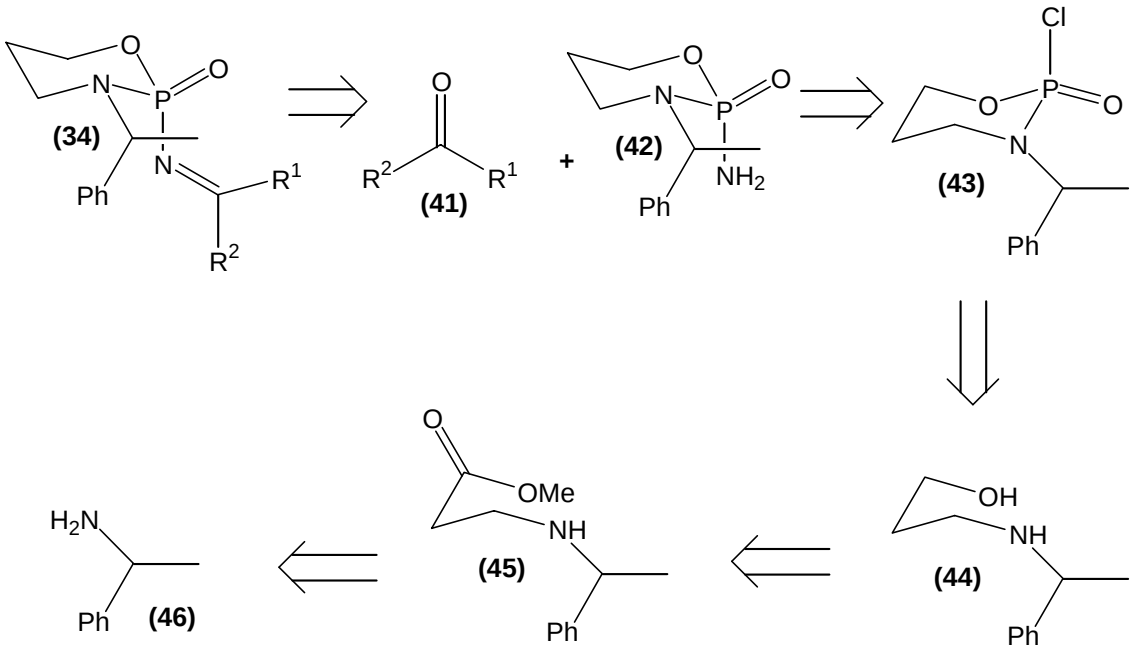
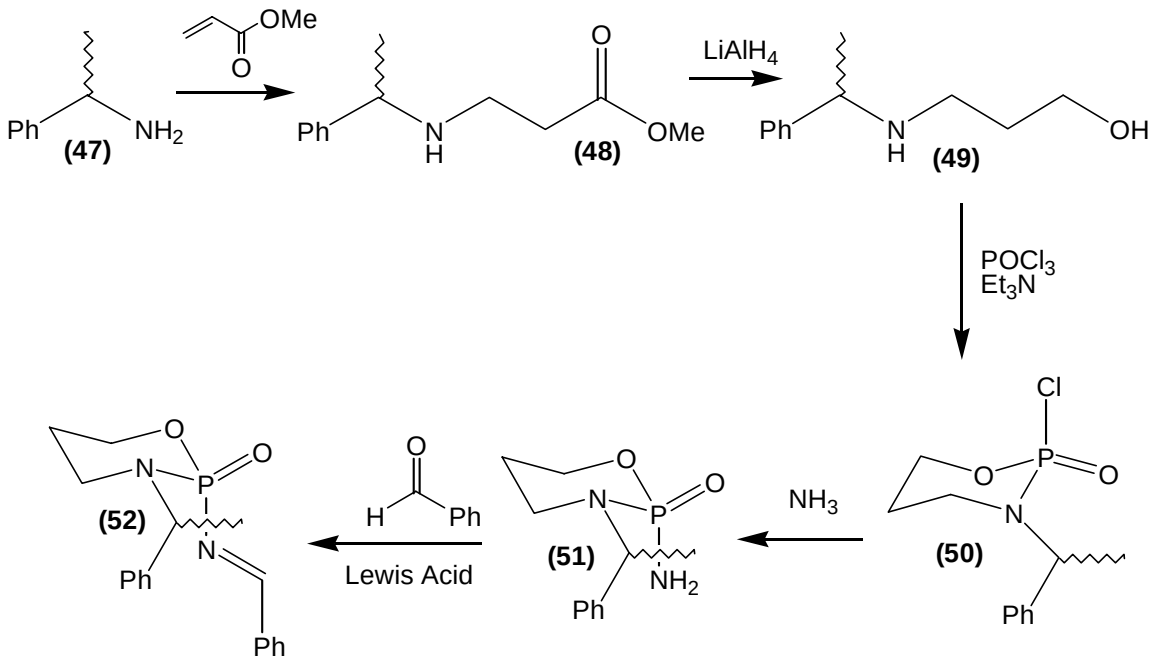


Figure 5

The proposed procedure for the synthesis of the racemic 2-imino-2-oxo-1,3,2-oxazaphosphorinane **(52)** is outlined below (Scheme 7). Condensation of *(RS)*-α-methylbenzylamine **(47)** with methyl acrylate yields the aminoester **(48)** which can be reduced by using lithium aluminium hydride. The resulting aminoalcohol **(49)** upon treatment with phosphorus oxytrichloride can be converted to the phosphoramidochloridate **(50)**, which yields the corresponding phosphorodiamidate **(51)** upon reaction with liquid ammonia. The key reaction in our synthetic sequence is the condensation of **(51)** with benzaldehyde. Based upon various literature precedents, which

will be outlined later, we envisaged that Lewis acid catalyst will be required in order to yield our synthetic target **(52)**.



Scheme 7

Following preparation of the benzaldehyde derived aldimine **(52)** the next objective is to use the same methodology to synthesize the corresponding enantiomerically pure 2-imino-2-oxo-1,3,2-oxazaphosphorinane derivatives (X=H) **(53a)** and **(54a)**. It is envisaged that other 4-substituted aromatic aldehydes could be employed to yield the related derivatives **(53b,c)** and **(54b,c)** (Figure 6).

Ketimines are a more challenging synthetic target due to the poor electrophilicity of ketones compared to aldehydes. Thus, ketimines **(55)** and **(56)** derived from acetophenone are our next synthetic target (Figure 7).

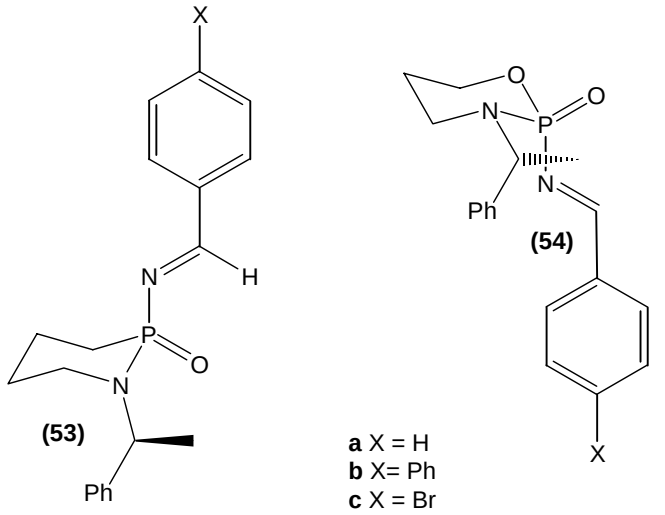


Figure 6

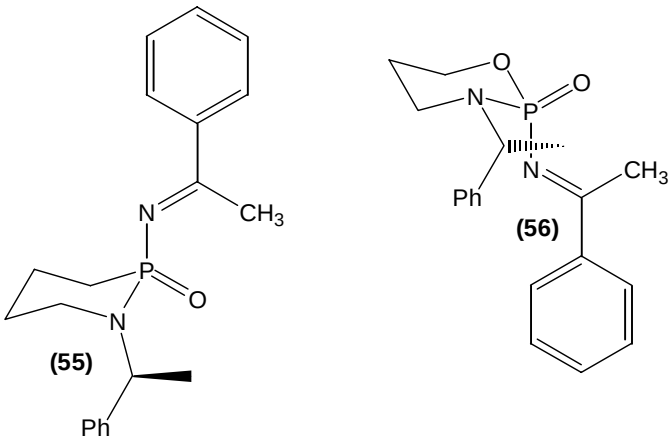


Figure 7

CHAPTER 2

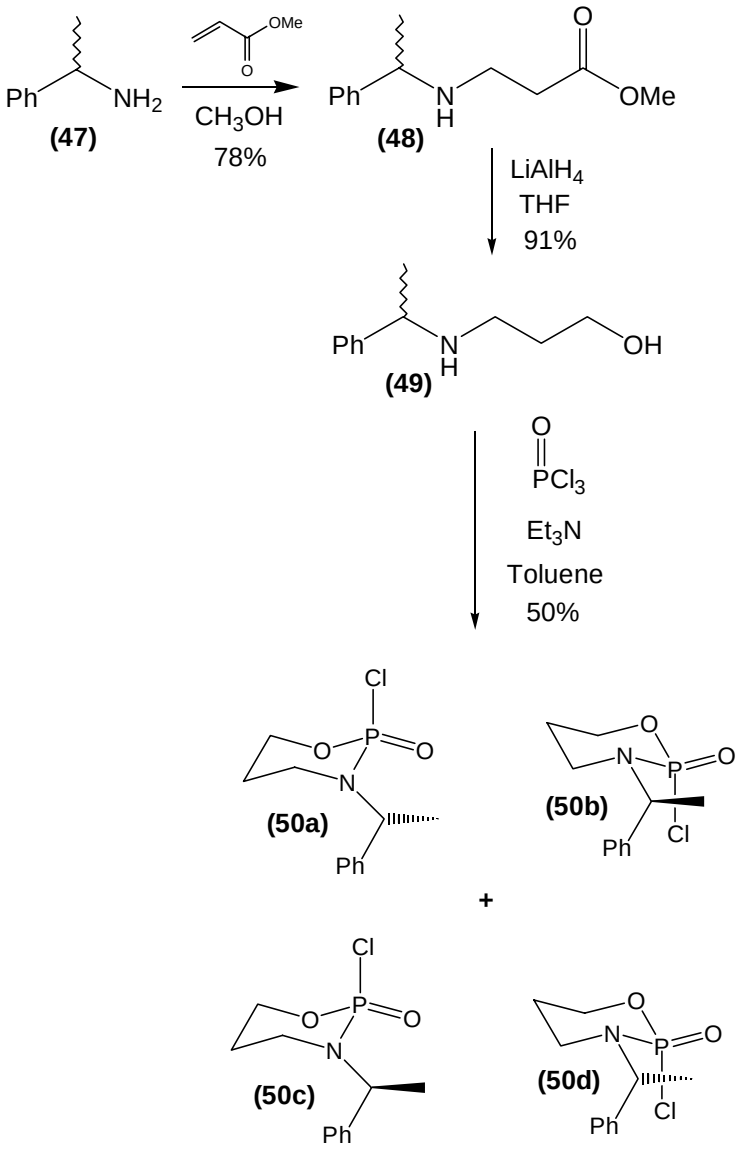
2. SYNTHESIS

2.1 Synthesis of 2-amino-2-oxo-1,3,2-oxazaphosphorinanes

2.1.1 Results and Discussion

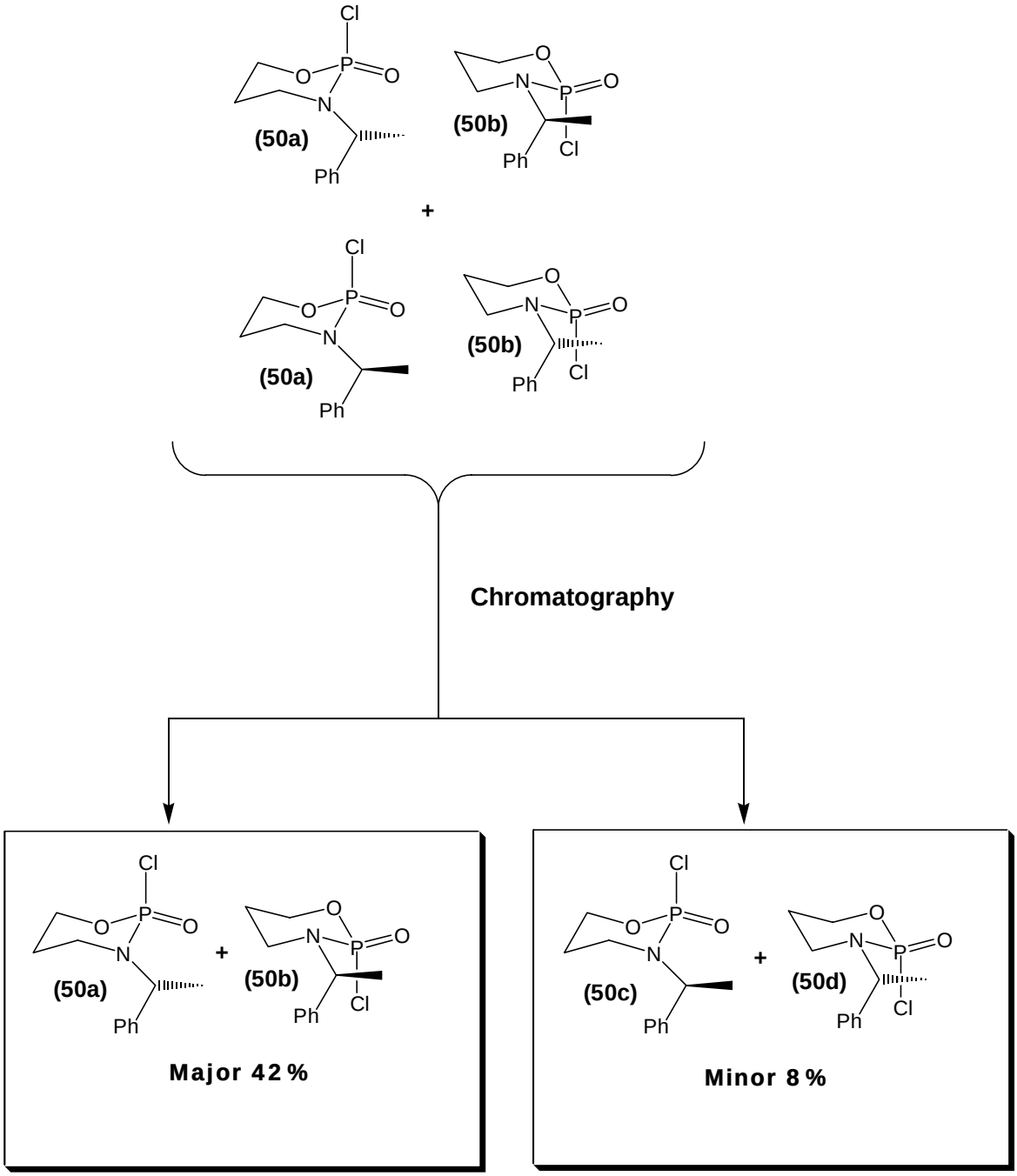
The conversion of racemic α-methylbenzylamine **(47)** to the corresponding phosphoramidochloridates **(50a,b,c,d)** is shown below (Scheme 8). 1,4-Addition of **(47)** with methyl acrylate occurred smoothly upon heating under reflux in methanol for three hours. Following removal of the solvent under reduced pressure the crude was purified by flash chromatography to yield the aminoester **(48)** with a 78% yield. The ester **(48)** was then reduced to the corresponding aminoalcohol **(49)** by heating under reflux in THF with 3.5 equivalents of lithium aluminum hydride.

The resulting amino alcohol **(49)** was then reacted with phosphorus oxytrichloride and triethylamine, as an acid scavenger, according to the known literature procedure. Four stereoisomers were obtained as two sets of enantiomeric pairs **(50a,b)** and **(50c,d).** ^{31}P NMR was utilized to follow the course of this cyclization reaction. Phosphorus oxytrichloride has a distinctive ^{31}P NMR peak at 5.12 ppm. The disappearance of this peak in the ^{31}P NMR of the crude reaction mixture clearly indicated completion of the reaction. Two new signals appeared at 9.60 ppm and 10.15 ppm respectively. Comparison of their integrals indicated that the two pairs of enantiomers were formed in a 1:10 ratio.



Scheme 8

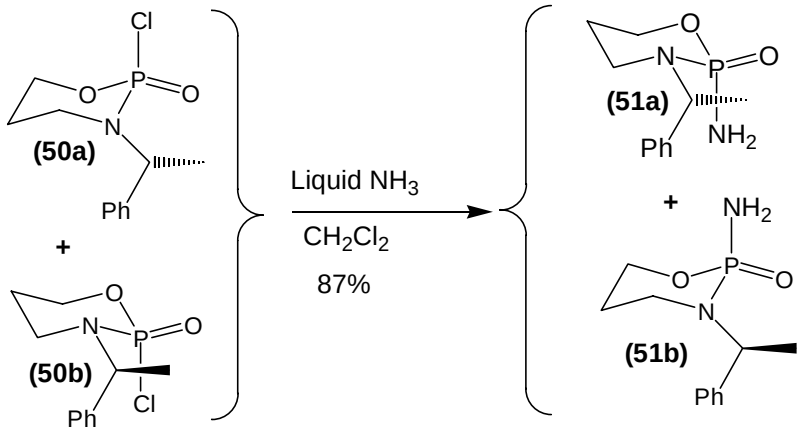
It should be emphasized at this point a very important advantage resulting from utilization of the *N*-α-methylbenzyl substituent. As this moiety contains a chiral center, the separation of the two diastereomeric phosphoramidochloridates **(50a,b)** and **(50c,d)** was possible using flash chromatography (Scheme 9).



Scheme 9

The major diastereoisomer **(50a,b)** was used to carry out the subsequent steps of the synthesis. Due to the unavailability of liquid ammonia, ammonium hydroxide (NH_4OH)

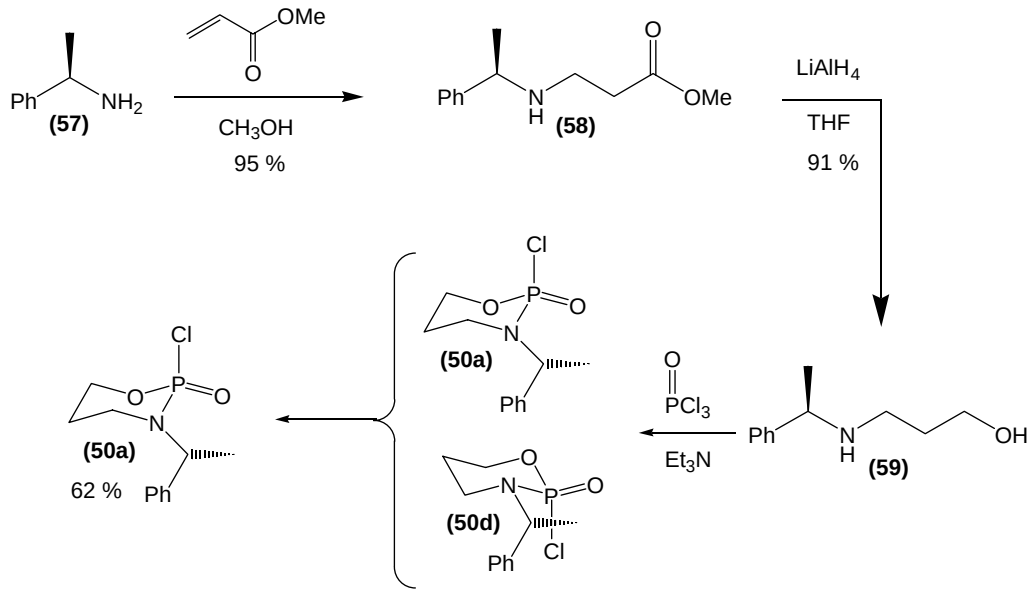
was heated in order to generate ammonia for the conversion of **(50a,b)** to phosphorodiamidate **(51a,b)** (Scheme 10). The reaction mixture was stirred overnight and ^{31}P NMR of the crude product showed complete conversion into the desired phosphorodiamidate **(51a,b)**. X-ray analysis confirmed the absolute stereochemistry and the conformation of this reaction product (see section 2.2).



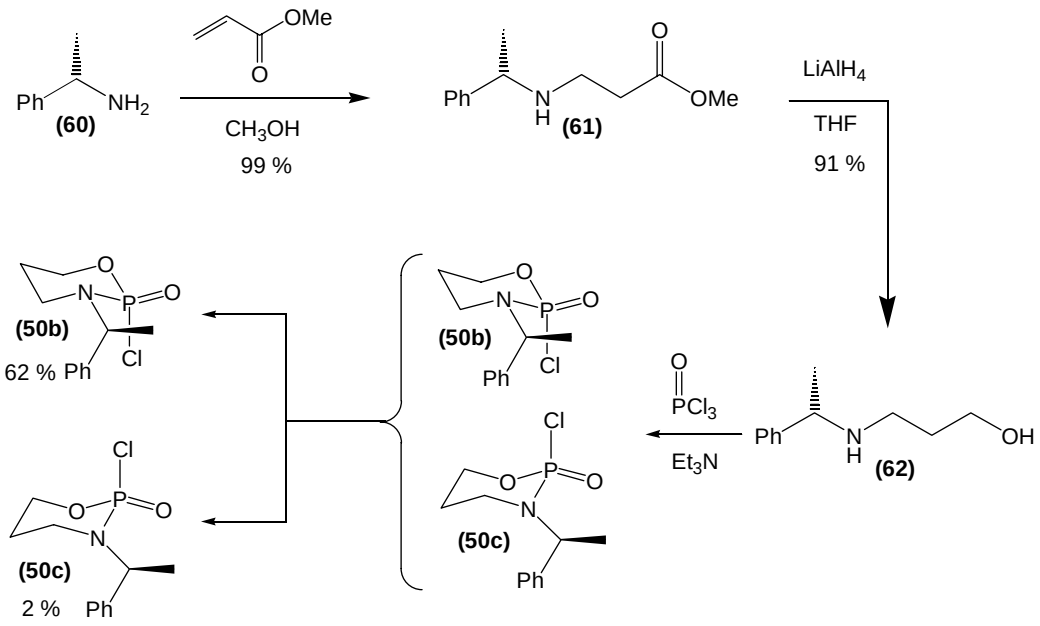
Scheme 10

The same approach was utilized with the enantiopure reagents *(R)-(+)*-α-methylbenzylamine **(57)** (Scheme 11) and *(S)-(-)*-α-methylbenzylamine **(60)** (Scheme 12). However, in both cases the diastereomeric mixture of phosphoramidochloridates, **(50a,d)** and **(50b,c)** respectively, were purified by recrystallization rather than column chromatography. Recrystallization of phosphoramidochloridates, **(50a,d),** from toluene and hexane, yielded the major diastereomer **(50a)** in improved yield (Scheme 11). Likewise, recrystallization of phosphoramidochloridates **(50b,c)** yielded the major diastereomer **(50b)** (Scheme 12). The resulting mother liquor was subjected to flash

chromatography which resulted in more of the major diasteroemer **(50b)** and a small amount of the minor diasteroemer **(50c)** being obtained.

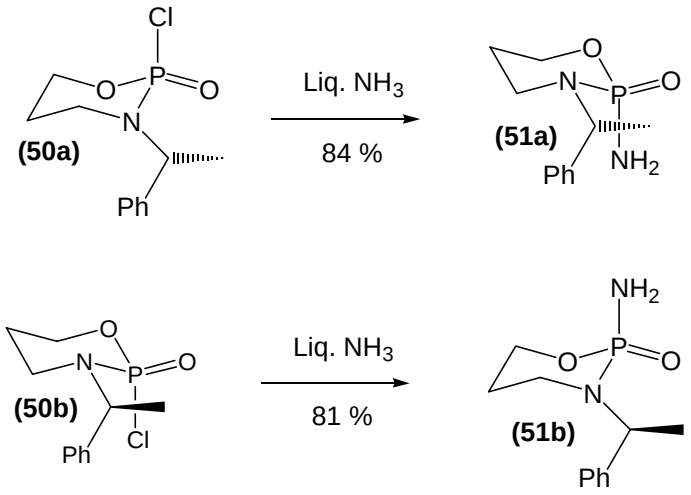


Scheme 11



Scheme 12

Both phosphoramidochloridates **(50a)** and **(50b)** then underwent ammonolysis to yield the corresponding phosphorodiamidates **(51a)** and **(51b)** respectively (Scheme 13).

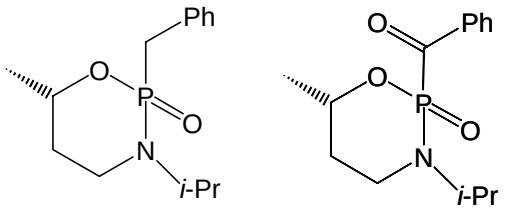


Scheme 13

2.2 X-ray Conformational Analysis of 2-oxo-1,3,2-oxazaphosphorinanes

2.2.1 Introduction

Study of the conformation of 2-oxo-1,3,2-oxazaphosphorinanes is important for three reasons. It is of basic interest to understand the effect on the conformational properties arising from the replacement, and substitution, of the carbon atoms of a cyclohexane ring by heteroatoms.[31,32] Secondly, this ring system is found in a number of anticancer drugs such as cyclophosphamide **(1a)**, isophosphamide **(1b)**, triphophosphamide **(1c)** (Figure 1) and therefore an understanding of this ring's preferred conformation contributes to the interpretation of these drugs' structure–activity relationships. [2] Finally, the conformation of 2-oxo-1,3,2-oxazaphosphorinanes is the basis of a number of models which predict asymmetric reactions of chiral phosphonamidates such as **(63)**[4,5] and **(64)**[14] (Figure 8).



(63) **(64)**

Figure 8

Thus, we were interested in obtaining information about the conformation of our target molecules phosphoramidochloridate **(43)** and phosphorodiamidate **(42)** (Figure 9). This will enable us to develop a conformational model of the corresponding imine **(34)**

which will assist us in explaining the stereochemical outcome of our proposed 1,4-adition reactions.

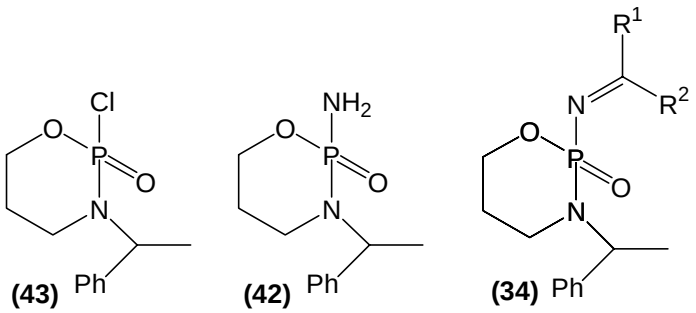
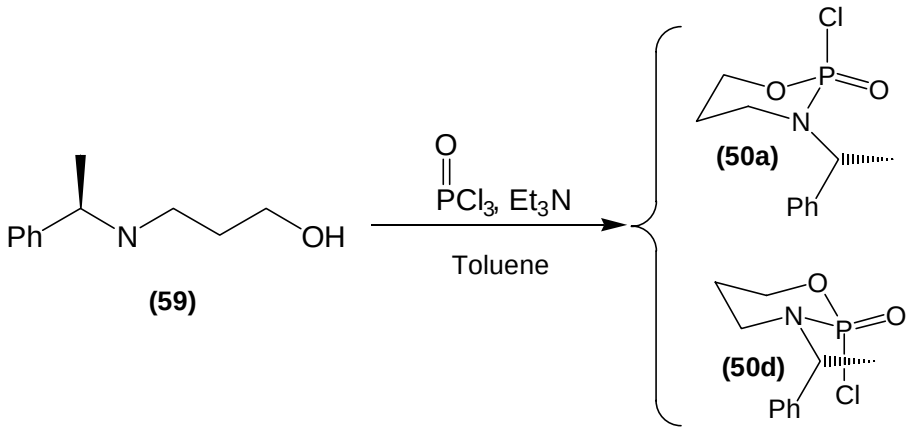


Figure 9

2.2.2 Results and Discussion

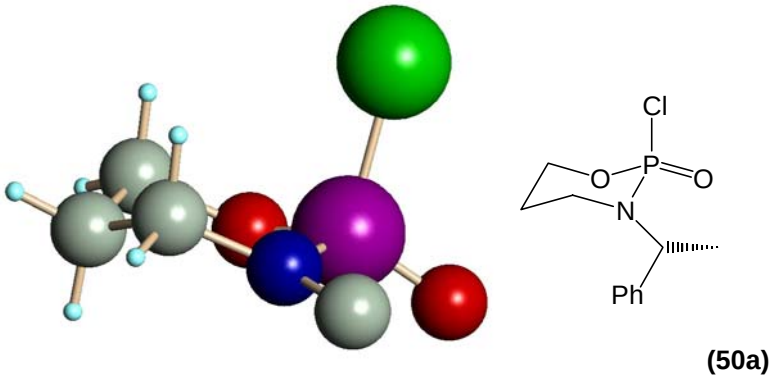
The cyclization of enantiomerically pure amino alcohol **(59)** with phosphorus oxytrichloride yielded two diastereomeric phosphoramidochloridates **(50a)** and **(50d)** (Scheme 14) in a 1:10 ratio, as determined by ^{31}P NMR of the crude product. It should be noted that there are no reports of X-Ray structures for these compounds in the literature. Thus, it was not clear which of these two diastereoisomers was the major and which was the minor reaction product.

Recrystallization of this diastereomeric mixture from toluene and hexane yielded the major phosphoramidochloridate in a diastereomerically pure form as white needles. We were able to obtain a single crystal X-ray of this diastereomer which unambiguously confirmed the major reaction product was diastereomer **(50a)**.



Scheme 14

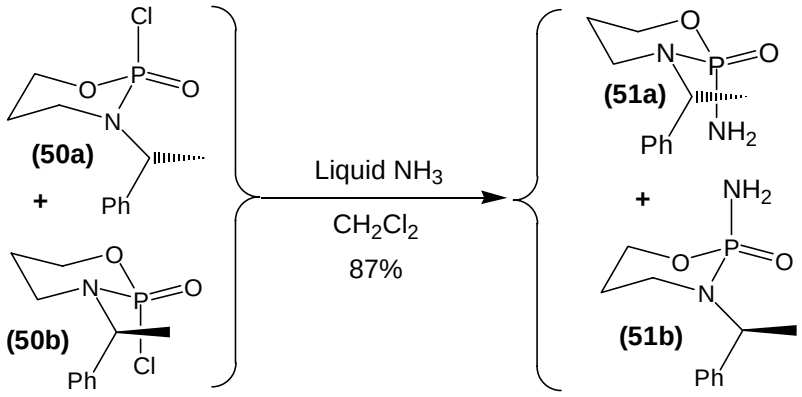
This X-ray (Figure 10) clearly indicates that the *exo* cyclic P=O is equatorial and the chlorine is axial. Note that the hydrogen and both methyl and phenyl groups of the *N*-α-methylbenzyl substituent have been removed for the sake of clarity.



(50a)

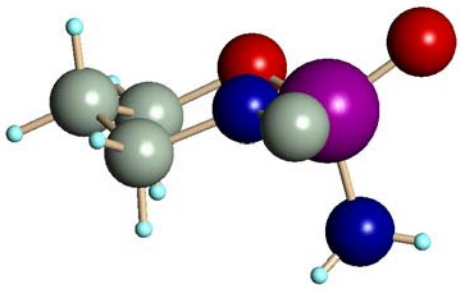
Figure 10

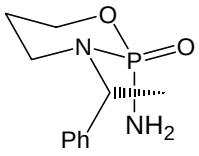
Amonolysis of the enantiomeric pair **(50a,b)** was followed by the usual work up, and yielded the crude phosphorodiamidate **(51a,b)** (Scheme 15).



Scheme 15

Purification was attempted by triturating the crude product with toluene. To our delight pure crystals of the enantiomeric pair **(51a,b)** were obtained and X-ray analysis unambiguously confirmed its structure. One half of the unit cell is showed for the sake of clarity (Figure 11). Once again the *exo* cyclic P=O is equatorial and the amino group is axial.





(51a)

Figure 11

2.2.3 Literature Precedents

Upon obtaining X-ray crystal structures for phosphoramidochloridate **(50a)** and phosphorodiamidate **(51a)** a more comprehensive literature survey was conducted. X-ray crystal structures were found for the following 2-oxo-1,3,2-oxazaphosphorinanes (Figure 12). Bentrude reported the conformation of 5,5-dimethyl-2-(dimethylamino)-2-oxo-1,3,2-oxazaphosphorinane **(65)**.[33] Stec reported the first crystal structure of 2-(S)-2-fluoro-oxo-3-[*(S)*-α-methylbenzyl]-1,3,2-oxazaphosphorinane **(66)**.[34] Recently, Afarinkia obtained X-ray crystal structures for the 2-aroyl-3-*N*-benzyl derivative **(67)** and the 2-aroyl-3-*N*-benzhydryl derivative **(68)**.[35] In all of the above examples the *exo* cyclic P=O was found to be equatorial whereas the other group was axial.

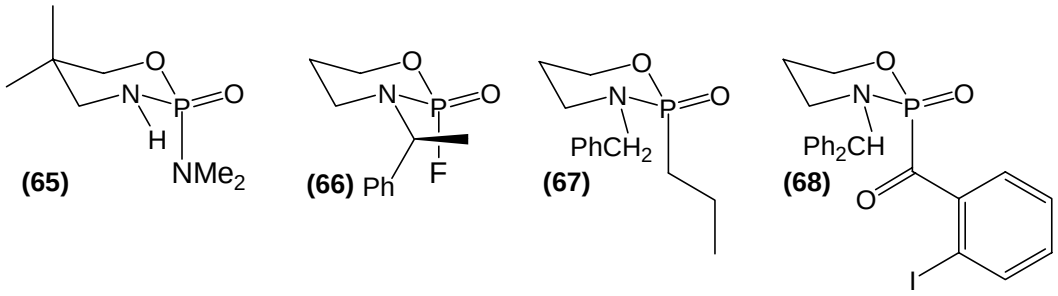


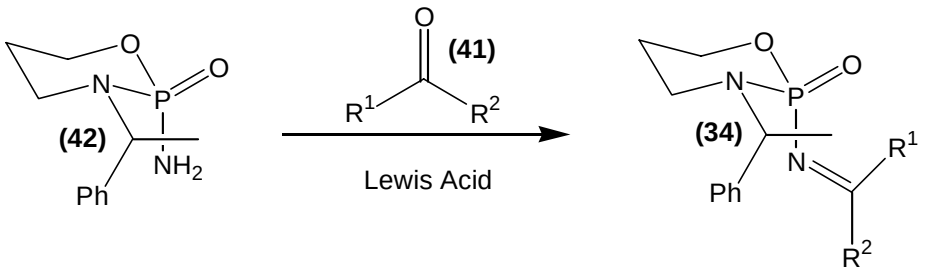
Figure 12

Thus, our brief conformational study yielded the same findings as previous studies on the related 2-oxo-1,3,2-oxazaphosphorinanes outlined above. The full crystal structures of **(50a)** and **(51a)**, including the *N*-α-methylbenzyl substituent, have been placed in appendix A.

2.3 Synthesis of 2-imino-2-oxo-1,3,2-oxazaphosphorinanes

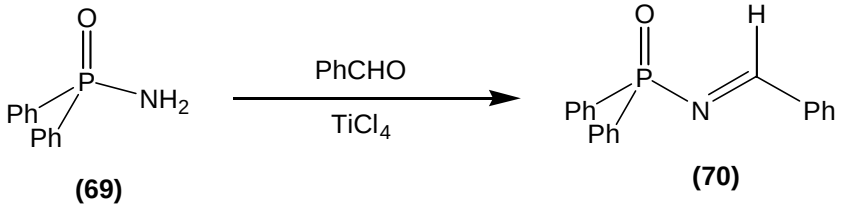
2.3.1 Synthesis of Aldimines

The key reaction in our synthetic sequence is the conversion of phosphorodiamidate (**42**) to our target 2-imino-2-oxo-1,3,2-oxazaphosphorinanes (**34**) (Scheme 16). Our objective was to develop methodology that would allow for efficient condensation of both aromatic aldehydes and ketones which are less electrophilic.



Scheme 16

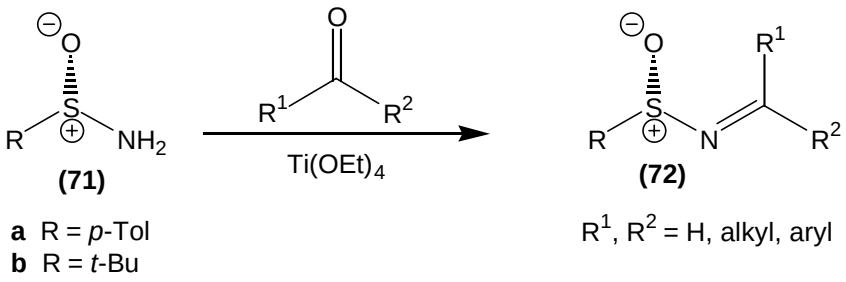
As our 2-imino-2-oxo-1,3,2-oxazaphosphorinanes (**34**) are a novel class of activated imines we sought literature precedents for the synthesis of related imine systems. Lovely and co-workers reported the preparation of *N*-diphenylphosphinoylimine **(70)** from the reaction of diphenylphosphinic amide **(69)** with benzaldehyde (Scheme 17).[36] However,



(Scheme 17)

this method was only suitable for the condensation of aromatic aldehydes and occurred only with moderate overall yields (35-58%).

Over the last 10 years extensive efforts had been made to develop various flexible approaches to the synthesis of *N*-sulfinylimines **(72)** from the corresponding *N*-sulfinamides **(71a,b)** (Scheme 18). Importantly, the utilization of titanium (IV) ethoxide as Lewis acid has allowed the synthesis of both aldimines and ketimines.[18,19]



(Scheme 18)

Thus, it was decided to try both of these methods for the synthesis of our target 2-imino-2-oxo-1,3,2-oxazaphosphorinanes (**34**).

2.3.1.1 Results and Discussion

Our first target was to synthesize the imine **(53a)** derived the condensation of the homochiral phosphorodiamidate **(51b)** with benzaldehyde (Scheme 19). Initially, we chose to employ the same reaction conditions that Ellman and Davis utilized for the synthesis of *N*-sulfinylimines.[18,19] Five equivalents of Lewis acid, $Ti(OEt)_4$, were used in order to activate the imine and to drive the reaction to completion. The reaction was

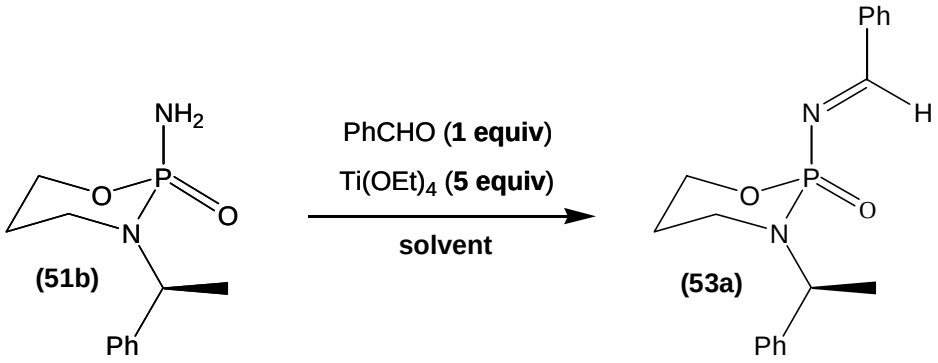
heated under reflux before quenching the cooled reaction mixture with water. The crude was then filtered through a pad of celite in order to remove the titanium (IV) salt.

^{1}H NMR and ^{31}P NMR was employed to study the outcome of this reaction. Imine formation was confirmed by the appearance of a characteristic doublet, due to $^{3}J_{PH}$ coupling, at 9.16 ppm in the ^{1}H NMR spectrum. Comparison of the integration of the phosphorodiamidate ^{31}P peak (11.41 ppm) and the new imine ^{31}P peak (9.67 ppm) allowed for the conversion to be determined.

2.3.1.1.1 Solvent Effect

Our initial experiments were conducted on a 10 mmol scale. When the reagents were heated under reflux with THF as the solvent a very low conversion was observed (entry 1, Table 1). Also five additional minor peaks were observed in the crude ^{31}P NMR. Thus, it was clear that the reaction was not clean. The same reaction was attempted at room temperature (entry 2, Table 1). However, both ^{1}H NMR and ^{31}P NMR indicated that the reaction still was not clean.

We were very happy to observe a cleaner reaction when dichloromethane was used as the solvent (entries 3 and 4, Table 1). Importantly, only two peaks for the phosphorodiamidate starting material and imine product were observed in the crude ^{31}P NMR. Likewise, the ^{1}H NMR spectrum clearly showed the characteristic doublet of the imine at 9.16 ppm. However, the conversion was still not satisfactory (37-40%).



Scheme 19

Table 1 The effect of solvent and temperature on the conversion of **(51b)** to **(53a)**

Entry	**Solvent**	**Temp**	**Time** (hrs)	**Conversion**[a] (%)
1	THF	Reflux	18	10
2	THF	25 ºC	26	23
3	DCM	Reflux	18	40
4	DCM	25 ºC	24	37

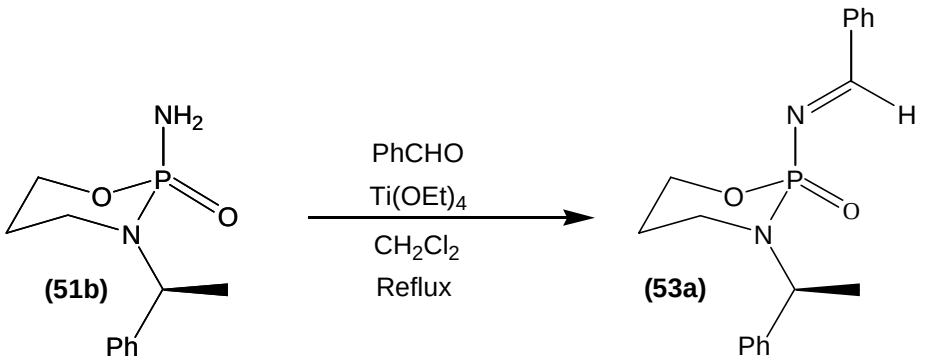
[a] as indicated by ^{31}P NMR of the crude product.

Thus, it was decided to further optimize this reaction using dichloromethane as the solvent prior to attempting purification by column chromatography.

2.3.1.1.2 Reaction Time and Ratios of Starting Material

Variation of the reaction time did not lead to a linear increase in the conversion (entries 1, 2 and 3, Table 2). The maximum conversion obtained was 70% following

heating under reflux for 12 hours (entry 2, Table 2). Utilization of two equivalents of benzaldehyde led to an improvement in the conversion (entries 3 and 4, Table 2). Upon heating under reflux for 24 hours the conversion increased to 86% (entry 5, Table 2).



Scheme 20

Table 2 The effect of reaction time and the ratio of reagents on the conversion of **(51b)** to **(53a)**

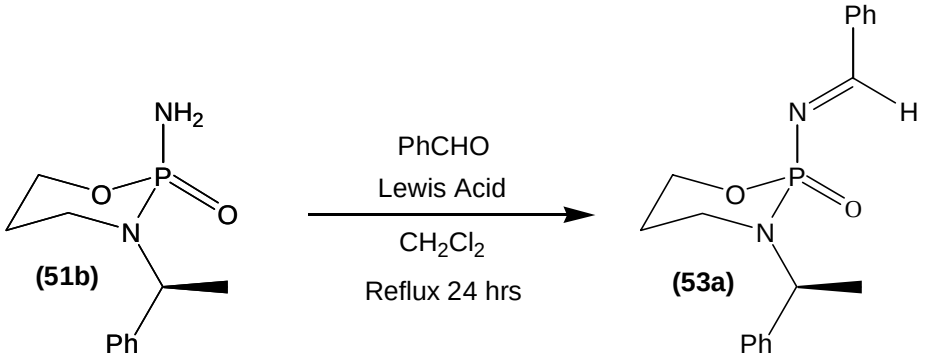
Entry	**Ratio** $P(O)NH_2 : PhCHO : Ti(OEt)_4$	**Time** (hrs)	**Conversion**[a] (%)
1	1 : 1 : 5	4	50
2	1 : 1 : 5	12	70
3	1 : 1 : 5	24	61
4	1 : 2 : 5	12	83
5	1 : 2 : 5	24	86

[a] as indicated by ^{31}P NMR of the crude product.

The non-linear improvement in conversion (entries 1, 2 and 3, Table 2) prompted us to speculate whether this reaction was reversible.

2.3.1.1.3 Effect of Lewis Acid

We then investigated the effect of the Lewis acid upon the conversion of **(51b)** to **(53a)** (Scheme 21). None of the Lewis acids used gave a conversion higher than the 86% conversion observed with $Ti(OEt)_4$ (entry 1, Table 3). The closely related $Ti(O^iPr)_4$ gave 77% conversion (entry 2, Table 3) whereas the strongly Lewis acidic $TiCl_4$ only resulted in a 43% conversion (entry 4, Table 3). The addition of 4Å Molecular sieves as an additional drying reagent proved unsuccessful with a much lower conversion being observed (entry 3, Table 3). Anhydrous copper (II) sulfate has been utilized as an effective drying agent and catalyst for the synthesis of *N*-sulfinamide derived aldimines.[19] However, no conversion was observed following heating under reflux for 24 hours in dichloromethane. Both ^1H and ^{31}P NMR indicated only the presence of recovered starting material (entries 5, and 6, Table 3).



Scheme 21

Table 3 The effect of Lewis acid on the conversion of **(51b)**to **(53a)**

Entry	**Lewis Acid**	**Ratio** $P(O)NH_2$: PhCHO : Lewis Acid	**Conversion**[a] (%)
1	$Ti(OEt)_4$	1 : 2 : 5	86
2	$Ti(O^iPr)_4$	1 : 2 : 5	77
3	$Ti(OEt)_4$ + 4Å Mol. Sieves	1 : 2 : 5	18
4	$TiCl_4$ [b]	1 : 2 : 5	43
5	$CuSO_4$	1 : 1.1 : 2.2	0
6	$CuSO_4$	1 : 2 : 5	0

[a] as indicated by ^{31}P NMR of the crude product.

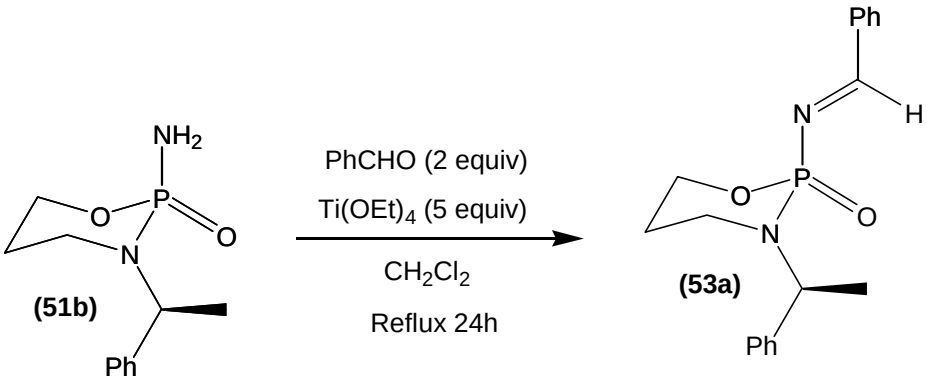
[b] Three equivalents of triethylamine (with respect to the $TiCl_4$) were utilized as an acid scavenger.

2.3.1.1.4 Workup Procedure

Following a review of our results it was found that there was a large difference in the conversion for reactions which had been heated under reflux in dichloromethane for 24 hours (entry 1, Table 4). We postulated that the reaction could be reversible with the aldimine product **(53a)** reverting back to the phosphorodiamidate **(51b)** and benzaldehyde. Thus, it was decided to follow the reaction more closely using ^{31}P NMR.

After 24 hours of heating under reflux an aliquot was taken from the reaction mixture prior to work up. ^{31}P NMR showed the presence of only one peak at 9.67 ppm for the aldimine **(53a)**. Importantly, no peak for the phosphorodiamidate starting material **(51b)** was observed which indicated that the reaction had gone to completion. This finding seemed to indicate that some hydrolysis of the aldimine product occurred during our work up procedure. Thus, a modified work up consisting of removing the solvent under reduced pressure was adopted. ^{31}P NMR analysis of the crude reaction mixture showed only one peak for the product indicating 100% conversion (entry 2, Table 4).

The excess $Ti(OEt)_4$ was readily removed from the product following column chromatography. However, it was more difficult to remove the excess benzaldehyde from the aldimine product and so the isolated yields were low. It should be noted that the aldimine product **(53a)** was very sensitive to hydrolysis. This was often observed even when left in $CDCl_3$ in a NMR tube for a few hours. Thus, it had to be stored without solvent under a nitrogen atmosphere in the fridge or used immediately for subsequent transformations (see 2.4).



Scheme 22

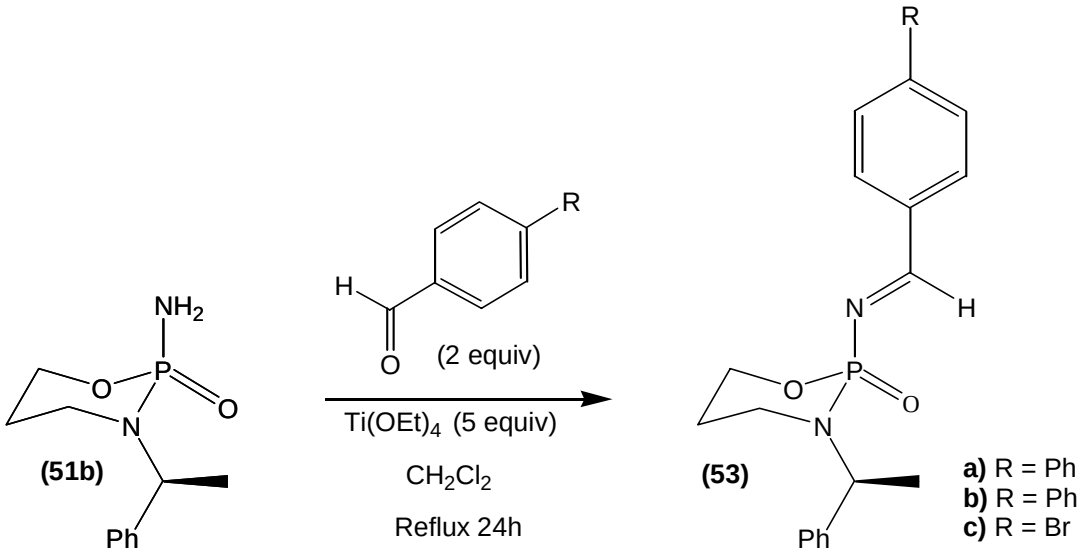
Table 4 The effect of the Work Up on the conversion of **(51b)**to **(53a)**

Entry	**WorkUp Procedure**	**^{31}P NMR**	**Conversion[a]** (%)
1	Quenching with water	2 peaks	60 – 86
2	Removing solvent under reduced pressure	One peak	100

[a] as indicated by ^{31}P NMR of the crude product.

2.3.2 Synthesis of Aldimines Derived from other Benzaldehyde Derivatives

Several other 4-substituted benzaldehyde derivatives (R= Ph, Br) were reacted with phosphorodiamidate **(51b)** using the modified work up procedure. The corresponding aldimines **(53b)** and **(53c)** were obtained (Scheme 23 and Table 5). In each case ^{31}P NMR showed 100% conversion. The ^{1}HNMR showed the distinctive doublet of the imine proton due to $^{3}J_{PH}$ coupling (27.1–32.3 Hz).



Scheme 23

Table 5 Aldimines derived from 4-substituted benzaldehydes

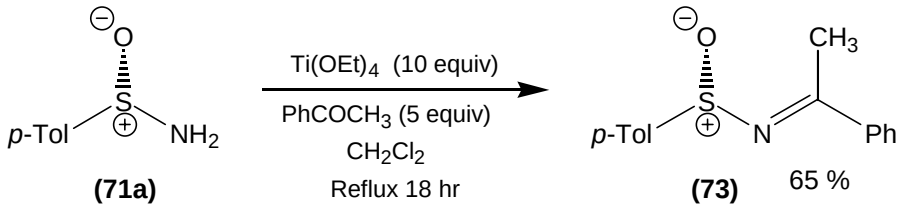
Entry	**R**	**^{1}H NMR** (–N=C***H***Ph)		**^{31}P NMR**	**Conversion[a] (%)**
		δ_H /ppm	$^{3}J_{PH}$/Hz	δ_P /ppm	
1	H	9.16	32.3	9.67	100
2	Br	9.03	27.1	9.34	100
3	Ph	9.12	32.3	9.82	100

[a] as indicated by ^{31}P NMR of the crude product.

2.3.3 Synthesis of Ketimines

2.3.3.1 Results and Discussion

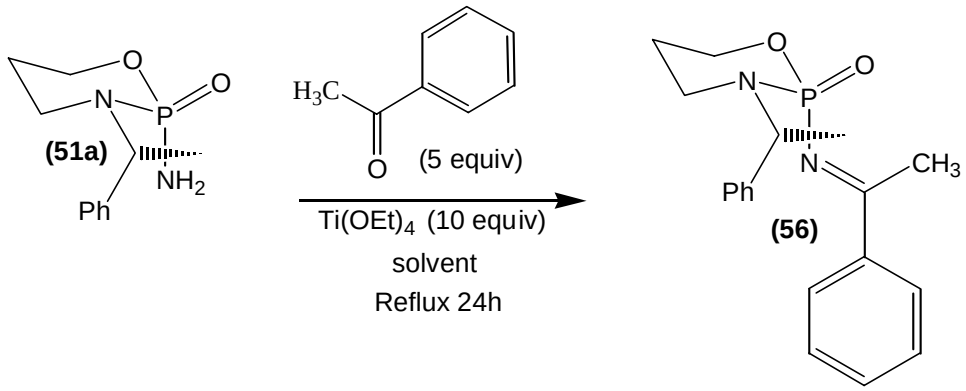
Ketimines are a more challenging synthetic target due to the poor electrophilicity of ketones compared to aldehydes. Lovely and co-workers were unable to apply their $TiCl_4$ mediated condensations to the synthesis of ketimines derived from diphenylphosphinic amide **(69)**. Only the competing aldol condensation product and recovered starting material were obtained.[36] However, Davis successfully utilized a large excess of $Ti(OEt)_4$ for the synthesis of ketimine **(73)** derived from *N*-sulfinamide **(71a)** (Scheme 24). Ten equivalents of Lewis acid and five equivalents of acetophenone were required in order for the reaction to go to completion. Importantly, no competing aldol condensation products were observed.[37]



Scheme 24

We utilized the same conditions as Davis for our attempted ketimine formation. Unfortunately, a very low conversion was observed when dichloromethane was used as the solvent (entry 1, Table 6). This was far lower than was observed using similar conditions for our aldimine formation (entry 1, Table 4). In order to improve the rate of reaction we wanted a higher boiling point solvent. As outlined previously THF did not yield a clean reaction (entries 1 and 2, Table 1). Thus, we decided to use toluene and were

delighted to observe a dramatic improvement in the conversion (entry 2, Table 6). When toluene was used in conjunction with the modified work up procedure 100% conversion was achieved (entry 3, Table 6). This ketimine **(56)** was more stable than the corresponding aldimine **(53a)**. However, once again the excess acetophenone proved difficult to separate from the ketimine product **(56)**. Thus, following chromatography the isolated yield was only 44%.



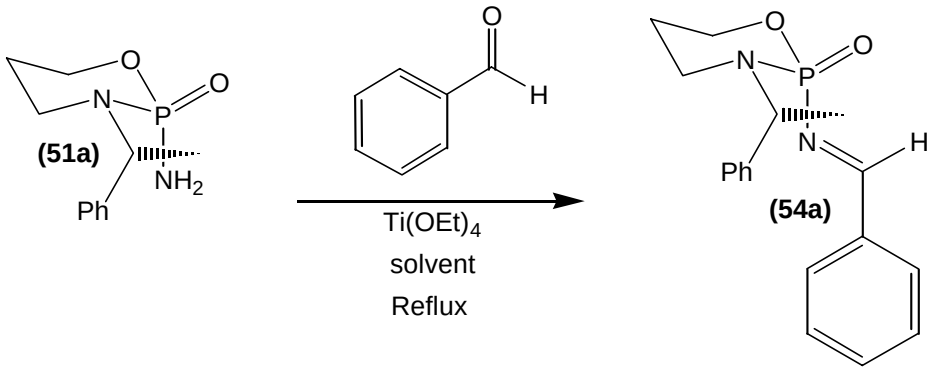
Scheme 25

Table 6 Synthesis of ketimine (**56**) derived from acetophenone

Entry	**Solvent**	**Work up**	**Conversion** (%)	**Isolated Yield %**
1	DCM	Quenching with water	17	9
2	Toluene	Quenching with water	81	42
3	Toluene	Removing solvent under reduced pressure	100	44

2.3.4 Synthesis of aldimines using toluene as the solvent

Our success in the ketimine synthesis caused us to revaluate our aldimine synthesis. We wanted to further optimize our best result (entry 1, Table 7) especially by reducing the required amount of benzaldehyde. When toluene was used as the solvent, with the same ratio of reagents, the reaction was complete after only 8 hours of heating under reflux (entry 2, Table 7). Heating under reflux in toluene for 24 hours, with only 1.1 equivalents of benzaldehyde, resulted in 95% conversion (entry 3, Table 7).



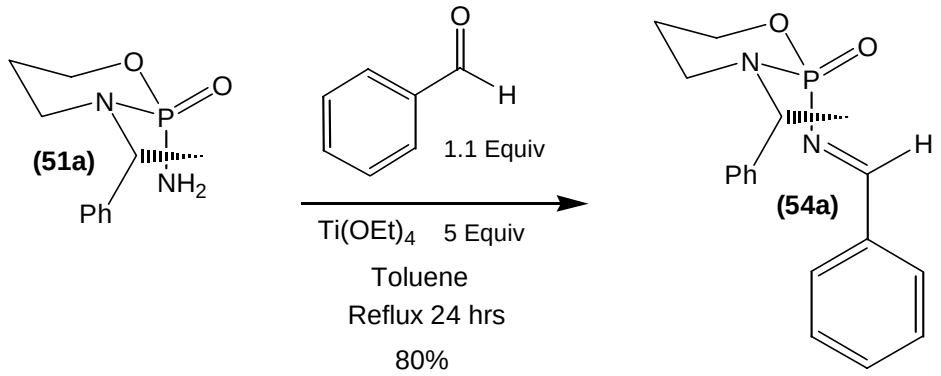
Scheme 26

Table 7 The effect of solvent on the conversion of **(51a)** to **(54a)**

Entry	**Solvent**	**Ratio** $P(O)NH_2$: PhCHO : $Ti(OEt)_4$	**Time** (Hrs)	**Conversion**[a] **(%)**
1	DCM	1:2:5	24	100
2	Toluene	1:2:5	8	100
3	Toluene	1:1.1:5	24	95

[a] as indicated by ^{31}P NMR of the crude product.

Thus, our most successful aldimine synthesis proceeded by heating under reflux in toluene for 24 hours, with only 1.1 equivalents of benzaldehyde. Purification using column chromatography yielded the desired aldimine (54a) with an isolated yield of 80% (Scheme 27).



Scheme 27

Due to the lack of time no further optimization was possible. However, we envisage that there is still scope to improve this reaction by reducing the amount of Lewis acid necessary for the reaction to go to completion. Thus, purification of our target aldimines by column chromatography will be easier. This will enable more material to be obtained for our 1,4-additions reactions to these aldimines.

2.4 Asymmetric 1,4-additions of Et_2AlCN to 2-imino-2-oxo-1,3,2-oxazaphosphorinanes

2.4.1 Results and Discussion

Two diastereomerically pure 2-imino-2-oxo-1,3,2-oxazaphosphorinanes, **(53a)** and **(54a)**, were synthesized (Figure 13).

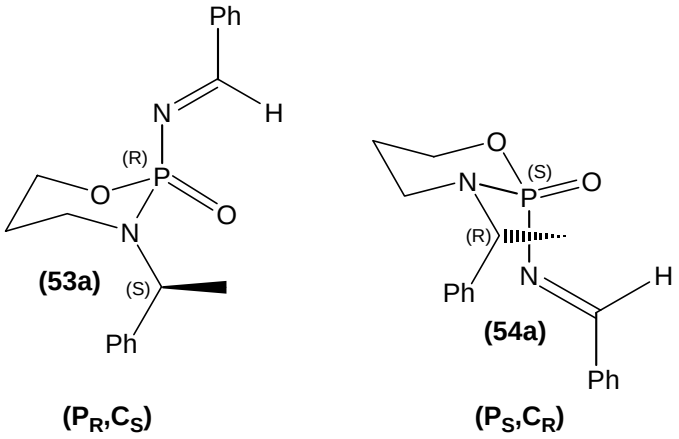
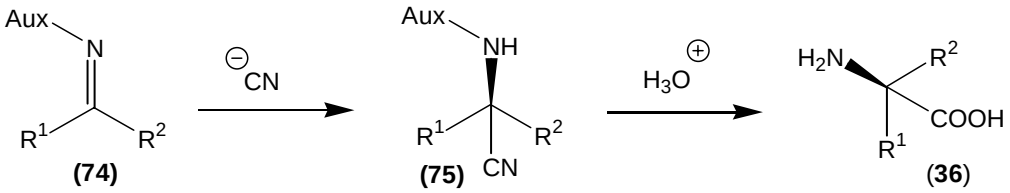


Figure 13

Unfortunately, these aldimines were not very stable at room temperature and underwent decomposition to the phosphorodiamidate starting material and benzaldehyde. This was clearly observed by both ^{1}H NMR and ^{31}P NMR. When this became apparent we decided to use these aldimines immediately after they were synthesized for subsequent transformations.

We wanted to investigate the diastereoselectivity of the 1,4 addition reaction of cyanide nucleophiles to this novel class of activated imine. Incorporation of the cyano

functional could allow for the synthesis of enantiomerically α-amino acids (**36**) following hydrolysis and removal of the chiral auxiliary (Scheme 28).

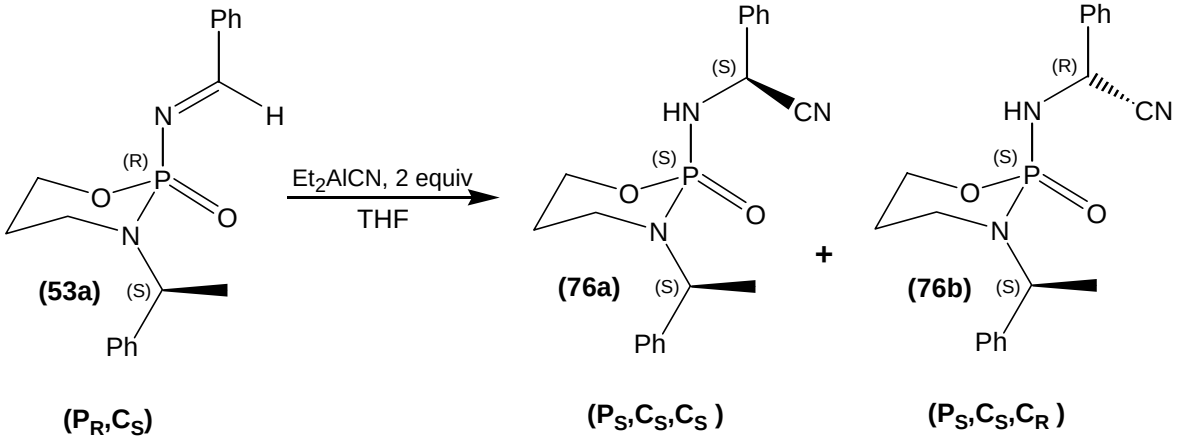


Scheme 28

Several small scale 1,4-additions of diethylaluminium cyanide to the (P_R, C_S) aldimine **(53a)** were attempted (Scheme 29). At first the addition was carried out at 25 ºC in THF using two equivalents of diethylaluminium cyanide (entry 1, Table 8). However, it was very difficult to follow the reaction by TLC as the spot for the addition product had a very similar R_f to that of the starting aldimine. After 2 hours, the reaction was quenched with saturated NH_4Cl solution and the crude product was analyzed. ^{1}H NMR showed that the doublet for the imine proton at 9.16 ppm had disappeared. Thus, the reaction had gone to completion as was also confirmed by ^{31}P NMR. Not only had the aldimine peak (9.67 ppm) disappeared but there were two new peaks at 7.59 and 7.87 ppm, respectively. Integration of these two peaks indicated that the ratio of these peaks was 0.40 : 1.0.

Thus, our first attempted 1,4-addition had proceeded with a moderate level of diastereoseletivity (43% de). The diastereoselectivity improved slightly (48% de) when the reaction was repeated at - 10 ºC (entry 2, Table 8). However, when we attempted to purify the crude reaction mixture by chromatography crystals started to form. Thus, this

mixture was recrystallized from ethyl acetate and hexane. We were delighted to obtain the major addition product in a diastereomerically pure form, albeit in a very small quantity (16mg) due to the small scale of this reaction. Thus, at this stage we were unable to assign this major product as either **(76a)** or **(76b)**. We hope to repeat this reaction on a larger scale so that sufficient diastereomerically pure material will be obtained. This will enable the absolute stereochemistry to be assigned following X-ray analysis.



(P_R,C_S) **(P_S,C_S,C_S)** **(P_S,C_S,C_R)**

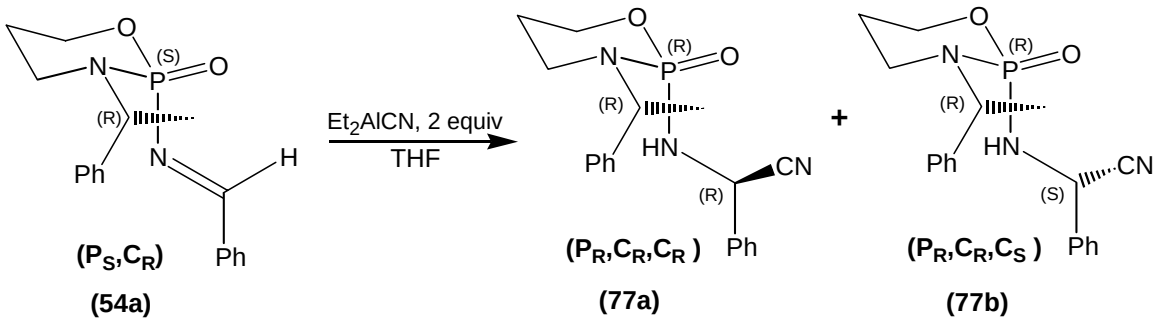
Scheme 29

Table 8 1,4-Addition of Et_2AlCN to (**53a**)

Entry	Time	Temp	% d.e
1	2 h	25 ºC	43
2	12 h	-10 ºC	48

Several small scale 1,4-additions of diethylaluminium cyanide to the (P_S, C_R) aldimine **(54a)** were also attempted (Scheme 29). Once again problems were encountered

in trying to follow the reaction by TLC. However, lower diastereoselectivities were observed for this (P_S, C_R) aldimine **(54a)** (entries 1 and 2, Table 9).



Scheme 30

Table 9 1,4-Addition of Et_2AlCN to (**54a**)

Entry	Time	Temp	% d.e
1	15 min	-10 ºC	18
2	12 h	-40 ºC	36

CHAPTER 3

3. EXPERIMENTAL

3.1 General Methods and Experimentation

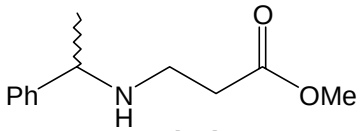
All the starting materials were used as received including solvents, without further purification unless otherwise stated. Specially dried (anhydrous) solvents were used where necessary. Glassware for moisture sensitive reactions were oven dried at 120-140 °C for at least three hours and cooled in a desiccator prior to use. Some of the reactions were run under inert atmosphere of nitrogen as stated.

Thin layer chromatography was frequently used to monitor reactions and to give qualitative determination of sample purity. TLC analysis carried out on Merck silica gel; 60 F_{254} plates and spots were visualized under a spectroline UV lamp operating at short and long wavelength ranges. Visualization was improved by dipping plates into alkaline potassium permanganate solution, followed by drying in a blast of hot air. Purification of the products was carried out either by recrystallization or by flash column chromatography. The column was packed with silica gel (Merk 9358) 60 mesh. Ethyl acetate, petroleum ether (boiling fraction 60-80) and hexane were used as eluting solvent, in volume-by-volume ratios as stated.

^{1}H NMR spectra were recorded using a Joel Lamda 500 MHz spectrometer. Spectra were internally referenced to using TMS. Deuterated chloroform ($CDCl_3$) was used as the

deuterated solvent for all spectra. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). All chemical shifts are reported in parts per million (ppm) and coupling constants (*J*) in hertz (Hz). ^{13}C NMR spectra where run on the same machine operating at 125 MHz under the same conditions. ^{31}P NMR spectra were run on the same machine operating at 202.35 MHz. 85% Phosphoric acid (H_3PO_4) in DMSO was used as internal standard for referencing ^{31}P NMR spectra.

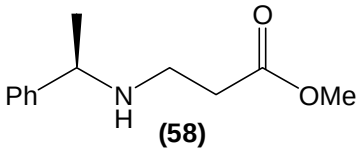
3.2 Experimental Procedures



(48)

Methyl 3-(1-phenylethylamino)propanoate (48)

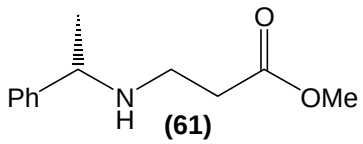
±-*(RS)*-α-Methylbenzylamine (1.41 g, 11.6 mmol), methylacrylate (0.960 g, 1.00 ml, 11.6 mmol) and methanol (15.0 ml) were added together and heated under reflux for 5 hours. Flash chromatography (petroleum ether : ethyl acetate 20:80) afforded methyl 3-(1-phenylethylamino)propanoate (**48**) (1.80 g, 78%) as a colorless oil.



(58)

Methyl 3-((*R*)-1-phenylethylamino)propanoate (58)

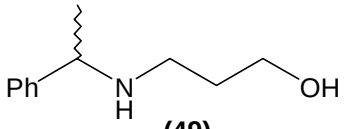
(R)-α-Methylbenzylamine (4.11 g, 34.0 mmol), methylacrylate (3.00 g, 3.10 ml, 34.0 mmol) and methanol (30.0 ml) were added together and heated under reflux for 5 hours. Evaporation of the solvent under reduced pressure yielded methyl 3-((*R*)-1-phenylethylamino)propanoate (**58**) (6.71 g, 95%) as colorless oil.



(61)

Methyl 3-((*S*)-1-phenylethylamino)propanoate (61)

(S)-α-Methylbenzylamine (4.12 g, 34.0 mmol), methylacrylate (2.92 g, 3.10 ml, 34.0 mmol) and methanol (30.0 ml) were added together and heated under reflux for 5 hours. Evaporation of the solvent under reduced pressure yielded methyl 3-((*S*)-1-phenylethylamino)propanoate (**61**) (6.70 g, 95%) as colorless oil.

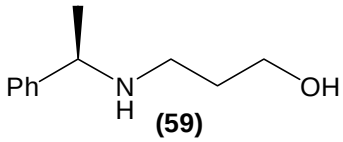


(49)

3-(1-phenylethylamino)propan-1-ol (49)

Methyl 3-(1-phenylethylamino)propanoate (**48**) (1.90 g, 9.10 mmol) was dissolved in THF (50 ml). Lithium aluminum hydride (1.73 g, 45.6 mmol) was added over 30 min. The reaction mixture was refluxed for 3 hours and then quenched (water/15% NaOH) after warming to room temperature. The precipitate was removed by filtration through a bed of celite. The crude product was purified by gradual elution with ($CHCl_3$:

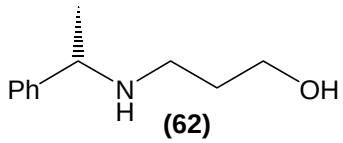
MeOH/NH_3 98:2) to remove the less polar product and then the polarity was increased (90:10) and the resulted 3-(1-phenylethylamino)propan-1-ol (**49**) (1.75 g, 91%) was isolated as a yellow oil.



(59)

3-((*R*)-1-phenylethylamino)propan-1-ol (59)

Methyl 3-((*R*)-1-phenylethylamino)propanoate **(58)** (5.53 g , 26.7 mmol) was dissolved in THF (130 ml). Lithium aluminum hydride (3.44 g, 90.7 mmol) was added slowly over 15 min. The reaction mixture was heated under reflux for 5 hours. The reaction mixture was refluxed for 5 h and then quenched (water/15% NaOH) after warming to room temperature. The precipitate was removed by filtration through a bed of celite and the solvent removed under reduced pressure to yield 3-((*R*)-1-phenylethylamino)propan-1-ol **(59)** (4.10 g, 91%) as a yellow oil.

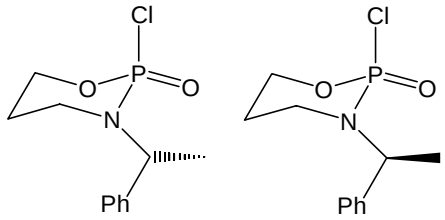


(62)

3-((*S*)-1-phenylethylamino)propan-1-ol (62)

Methyl 3-((*S*)-1-phenylethylamino)propanoate (**61**) (5.53 g, 26.7 mmol) was dissolved in THF (130 ml). Lithium aluminum hydride (3.44 g, 90.7 mmol) was added over 15 min. The reaction mixture was refluxed for 5 hours and then quenched (water/15% NaOH)

after warming to room temperature. The precipitate was removed by filtration through a bed of celite and the solvent removed under reduced pressure to yield 3-((*S*)-1-phenylethylamino)propan-1-ol (**62**) (4.10 g, 91%) as a yellow oil.

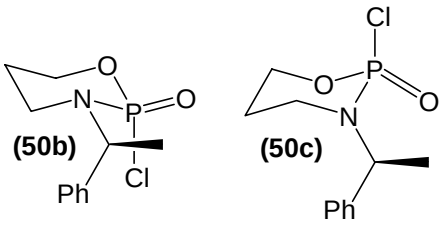


(50a) Racemic **(50c) Racemic**

Racemic (2*R*)-chloro-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (50a) and its diastereomer racemic (2*R*)-chloro-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (50c):

To a cooled solution (-10ºC) of phosphorus oxytrichloride (1.27 g, 0.800 ml, 8.30 mmol) and triethylamine (1.70 g, 2.40 ml, 16.6 mmol) in toluene (50 ml) was added a solution of 3-(1-phenylethylamino)propan-1-ol (**49**) (1.50 g, 8.30 mmol) in toluene (10 ml). The temperature was maintained at -10 to 0 ºC during the addition and for additional 30 min. After being allowed to warm to room temperature, the mixture was filtered through celite. Evaporation of the solvent under reduced pressure yielded the crude product as colorless semicrystalline mixture (2.0 g, 91%). The two diastereoisomers were separated by column chromatography using ethyl acetate / petroleum ether solution (25:75) and yielded the major diastereomer racemic (2*R*)-chloro-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (**50a**) (0.92 g, 42%) as a white semicrystalline solid, δ_P (202.35 MHz, $CDCl_3$) 9.60; δ_H (500 MHz; $CDCl_3$) 1.50 (3H, d, *J* 7.00 Hz, CHC*H*$_3$), 1.65-1.68

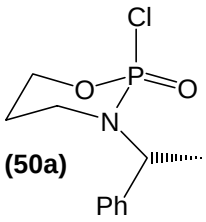
(1H, m, one of CH_2CH$_2$O), 1.92-2.02 (1H, m, remaining one of CH_2CH$_2$O), 2.47-2.64 (1H, m, one of NCH_2CH$_2$), 2.92-3.03 (1H, m, remaining one of NCH_2CH$_2$), 4.16-4.33 (2H, m, CH_2O), 4.77-4.83 (1H, m, C*H*CH$_3$), 7.17-7.27 (5H, m, C6H5); δ_C (125 MHz; $CDCl_3$) 19.1, 26.2, 42.4, 55.7, 70.4, 127.4, 127.5, 128.1, 138.9; and the minor diastereomer racemic (2*R*)-chloro-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (**50c**) (0.18 g, 8%) as a brown oil, δ_P (202.35 MHz, $CDCl_3$) 10.15; δ_H (500 MHz; $CDCl_3$) 1.56 (3H, d, *J* 7.00 Hz, CHCH_3), 1.66-1.70 (1H, m, one of CH_2CH$_2$O), 1.86-1.96 (1H, m, remaining one of CH_2CH$_2$O), 2.79-2.90 (1H, m, one of NCH_2CH$_2$), 3.05-3.02 (1H, m, remaining one of NCH_2CH$_2$), 4.38-4.47 (2H, m, CH_2O), 5.13-5.21 (1H, m, C*H*CH$_3$), 7.27-7.43 (5H, m, C6H5); δ_C (125 MHz; $CDCl_3$) 14.1, 26.0, 40.3, 53.0, 70.7, 127.3, 127.5, 128.3, 139.8



(2*S*)-Chloro-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (50b) and its diastereomer (2*R*)-chloro-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (50c) :

To a cooled solution (-10ºC) of phosphorus oxytrichloride (5.10 g, 3.10 ml, 33.1 mmol) and triethylamine (6.70 g, 9.30 ml, 66.1 mmol) in toluene (175 ml) was added a solution of 3-((*S*)-1-phenylethylamino)propan-1-ol **(62)** (5.90 g, 33.1 mmol) in toluene (25.0 ml).

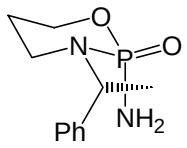
The temperature was maintained at -10 to 0 ºC during the addition and for additional 30 min. After being allowed to warm to room temperature, the mixture was filtered through celite. Evaporation of the solvent under reduced pressure yielded the crude product as colorless semicrystalline mixture (7.40 g, 89%). This was dissolved in toluene (5.00 ml). Hexane (10.0 ml) was added portionwise and the solution was stored at 4ºC for 4 hour. The major diastereomer (2*S*)-chloro-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (**50b**) (5.30 g, 62%) was obtained as a colorless needles: m.p 71-73 ºC; δ_P (202.35 MHz, $CDCl_3$) 9.63; δ_H (500 MHz; $CDCl_3$) 1.62 (3H, d, *J* 7.00 Hz, CHC*H*$_3$), 1.73-1.76 (1H, m, one of C*H*$_2$CH$_2$O), 2.06-2.17 (1H, m, remaining one of C*H*$_2$CH$_2$O), 2.65-2.72 (1H, m, one of NC*H*$_2$CH$_2$), 3.00-3.09 (1H, m, remaining one of NC*H*$_2$CH$_2$), 4.31-4.43 (2H, m, C*H*$_2$O), 4.90-4.93 (1H, m, C*H*CH$_3$), 7.28-7.44 (5H, m, C6H5). The mother liquor was concentrated and flash chromatography using ethyl acetate / petroleum ether solution (25:75) afforded the minor diastereomer (2*R*)-chloro-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (**50c**) (0.18 g, 2%) as brown oil; δ_P (202.35 MHz, $CDCl_3$) 10.22; δ_H (500 MHz; $CDCl_3$) 1.48 (3H, d, *J* 7.00 Hz, CHC*H*$_3$), 1.59-1.62 (1H, m, one of C*H*$_2$CH$_2$O), 1.82-1.92 (1H, m, remaining one of C*H*$_2$CH$_2$O), 2.77-2.83 (1H, m, one of NC*H*$_2$CH$_2$), 2.98-3.00 (1H, m, remaining one of NC*H*$_2$CH$_2$), 4.31-4.35 (2H, m, C*H*$_2$O), 5.10-5.18 (1H, m, C*H*CH$_3$), 7.19-7.35 (5H, m, C6H5); δ_C (125 MHz; $CDCl_3$) 15.04, 26.75, 41.30, 53.80, 71.92, 127.95, 128.3, 129.12, 140.8



(50a)

(2*R*)-Chloro-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (50a)

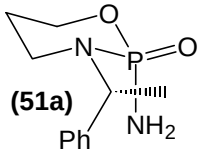
To a cooled solution (-10ºC) of phosphorus oxytrichloride (3.85 g, 2.34 ml, 25.1 mmol) and triethylamine (5.10 g, 7.03 ml, 50.2 mmol) in toluene (150 ml) was added a solution of 3-((*R*)-1-phenylethylamino)propan-1-ol **(59)** (4.50g, 25.1 mol) in toluene (25 ml). The temperature was maintained at -10 to 0 ºC during the addition and for additional 30 min. After being allowed to room temperature the mixture was filtered through celite. Evaporation of the solvent at reduced pressure gave a colorless semicrystalline mixture (6.20 g, 95%). This was dissolved in toluene (4.00 ml), hexane (8.00 ml) was added portionwise and the solution was stored at 4ºC for 4 hours. (2*R*)-Chloro-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (**50a**) (4.00 g, 62%) was obtained as colorless needles, m.p 71-73 ºC; δ_P (202.35 MHz, $CDCl_3$) 9.63; δ_H (500 MHz; $CDCl_3$) 1.60 (3H, d, *J* 7.00 Hz, CHC*H*$_3$), 1.71-1.74 (1H, m, one of C*H*$_2$CH$_2$O), 1.98-2.15 (1H, m, remaining one of C*H*$_2$CH$_2$O), 2.65-2.72 (1H, m, one of NC*H*$_2$CH$_2$), 2.99-3.12 (1H, m, remaining one of NC*H*$_2$CH$_2$), 4.28-4.44 (2H, m, C*H*$_2$O), 4.88-4.94 (1H, m, C*H*CH$_3$), 7.26-7.38 (5H, m, C6H5).



(51a) Racemic

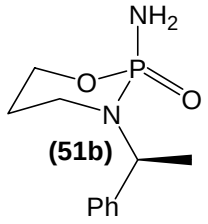
Racemic (*R*)-amino-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (51a)

Racemic (2*R*)-chloro-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane **(50a)** (0.500 g, 1.90 mmol) was dissolved in dichloromethane (20 ml) and the solution was cooled to -63 ºC. Excess liquid ammonia was added to the reaction vessel and the solution was stirred at -63°C for one hour and then allowed to warm to room temperature and stirred overnight. The crude was filtered through a bed of celite and washed with ethyl acetate (5.00 ml) , the filtrate was evaporated and recrystallized from hot toluene to yield racemic 2(*R*)-amino-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (**51a**) (0.40 g, 87%) as a white solid; δ_P (202.35 MHz, $CDCl_3$) 11.41; δ_H (500 MHz; $CDCl_3$) 1.53 (3H, d, *J* 7.05 Hz, CHC*H*$_3$), 1.64-1.67 (2H, C*H*$_2$CH$_2$O), 2.74-2.81 (3H, m, N*H*$_2$ and one of NC*H*$_2$CH$_2$), 2.95-3.02 (1H, m, remaining one of NC*H*$_2$CH$_2$), 4.17-4.28 (2H, m, C*H*$_2$O), 4.99-5.06 (1H, m, C*H*CH$_3$), 7.24-7.53 (5H, m, C6H5); δ_C (125 MHz; $CDCl_3$) 16.8, 26.5, 40.5, 52.7, 67.3, 126.9, 127.7, 128.0, 141.2



2(*R*)-Amino-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (51a)

(2*R*)-Chloro-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (**50a**) (4.20 g, 16.0 mmol) was dissolved in dichloromethane (40 ml) and the solution was cooled to -63 ºC. Excess liquid ammonia was added to the reaction vessel and the solution was stirred at -63°C for one hour and then allowed to warm to room temperature and stirred overnight. The crude was filtered through a bed of celite and washed with ethyl acetate (20.0 ml) , the filtrate was evaporated and recrystallized from hot toluene to yield 2-(*R*)-amino-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (**51a**) (3.25 g, 84%) as a white solid; δ_P (202.35 MHz, $CDCl_3$) 11.41; δ_H (500 MHz; $CDCl_3$) 1.53 (3H, d, *J* 7.05 Hz, CHC*H*$_3$), 1.64-1.70 (2H, C*H*$_2$CH$_2$O), 2.73-2.84 (3H, m, N*H*$_2$ and one of NC*H*$_2$CH$_2$), 2.95-3.02 (1H, m, remaining one of NC*H*$_2$CH$_2$), 4.17-4.29 (2H, m, C*H*$_2$O), 4.99-5.05 (1H, m, C*H*CH$_3$), 7.24-7.56 (5H, m, C6H5); δ_C (125 MHz; $CDCl_3$) 17.9, 27.5, 41.7, 53.9, 68.4, 128.1, 128.7, 129.1, 142.1

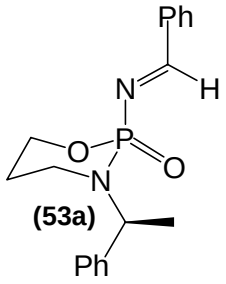


(51b)

2(*S*)-Amino-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (51b)

(2*S*)-Chloro-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (**50b**) (3.10 g, 16.0 mmol) was dissolved in dichloromethane (40.0 ml) and the solution was cooled to -63 ºC. Excess liquid ammonia was added to the reaction vessel and the solution was stirred at -63°C for one hour and then allowed to warm to room temperature and stirred overnight.

The crude was filtered through a bed of celite and washed with ethyl acetate (20.0 ml) , the filtrate was evaporated and recrystallized from hot toluene to yield 2(*S*)-amino-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphrinane (**51b**) (2.23 g, 81%) as a white solid; δ_P (202.35 MHz, $CDCl_3$) 11.51; δ_H (500 MHz; $CDCl_3$) 1.53 (3H, d, *J* 7.00 Hz, CHC*H*$_3$), 1.61-1.71 (2H, C*H*$_2$CH$_2$O), 2.73-2.80 (1H, m, one of NC*H*$_2$CH$_2$), 2.80 (2H, broad, m, N*H*$_2$), 2.95-3.02 (1H, m, remaining one of NC*H*$_2$CH$_2$), 4.17-4.29 (2H, m, C*H*$_2$O), 4.99-5.06 (1H, m, C*H*CH$_3$), 7.14-7.53 (5H, m, C6H5).



(53a)

3-[(*S*)-α-Methylbenzyl]-2(*R*)-oxo-2-[(phenylmethylene)amino]-1,3,2-oxazaphosphorinane (53a)

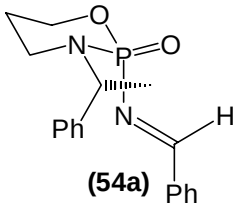
Method (A):

In an oven-dried single-necked 50 ml round-bottom flask equipped with a magnetic stirring bar and reflux condenser was placed 2(*S*)-amino-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphrinane (**51b**) (77.0 mg, 0.321 mmol). Then it was dissolved in dichloromethane (7.00 ml). Benzaldehyde (68.1 mg, 66.0 µl, 0.641 mmol) and titanium (IV) ethoxide (400 µl, 1.60 mmol) were added to the solution by syringe. The reaction mixture was refluxed for 24 h and cooled to 0 °C, H_2O (7.00 ml) was added, and the

solution was filtered through celite and washed with ethyl acetate (10.0 ml). The phases were separated, and the organic phase was washed with brine (5.00 ml), dried over magnesium sulphate, filtered through celite. The solvent was removed under reduced pressure. Flash chromatography (EtOAc : hexane, 25:75) afforded 3-[(*S*)-α-methylbenzyl]-2(*R*)-oxo-2-[(phenylmethylene)amino]-1,3,2-oxazaphosphorinane (**53a**) **(**0.041 g, 39%) as a colorless oil; δ_P (202.35 MHz, $CDCl_3$) 9.67; δ_H (500 MHz; $CDCl_3$) 1.39 (3H, d, *J* 7.00 Hz, CHC*H*$_3$), 1.68-1.71 (1H, m, one of C*H*$_2$CH$_2$O), 1.94-2.04 (1H, m, remaining one of C*H*$_2$CH$_2$O), 2.81-2.88 (1H, m, one of NC*H*$_2$CH$_2$), 3.32.-3.3.37 (1H, m, remaining one of NC*H*$_2$CH$_2$), 4.33-4.39 (1H, m, one of C*H*$_2$O), 4.56-4.62 (1H, m, remaining one of C*H*$_2$O), 5.02-5.08 (1H, m, C*H*CH$_3$), 7.24-7.96 (10H, m, Ar*H*), 9.16 (1H, d, *J* 32.3 Hz, NC*H*Ph).

Method (B):

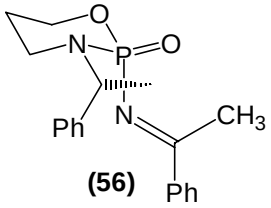
In an oven-dried single-necked 50 ml round-bottom flask equipped with a magnetic stirring bar and reflux condenser was placed 2(*S*)-amino-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphrinane (**51b**) (68.5 mg, 0.285 mmol). Then it was dissolved in dichloromethane (7.00 ml). Benzaldehyde (60.6 mg, 58 μl, 0.570 mmol) and titanium (IV) ethoxide (300 μl, 1.43 mmol) were added to the solution by syringe. The reaction mixture was refluxed for 24 h and cooled to room temperature. The solvent was removed under reduced pressure. Flash chromatography (EtOAc : hexane, 25:75) afforded 3-[(*S*)-α-methylbenzyl]-2(*R*)-oxo-2-[(phenylmethylene)amino]-1,3,2-oxazaphosphorinane (**53a**) **(**0.090 g, 96%) as white semicrystalline solid.



(54a)

3-[(*R*)-α-Methylbenzyl]-2(*S*)-oxo-2-[(phenylmethylene)amino]-1,3,2-oxazaphosphorinane (54a)

A similar procedure using 2-(*R*)-amino-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (**51a**) (246 mg, 1.025 mmol), dichloromethane (20.0 ml), benzaldehyde (218 mg, 209 μl, 2.05 mmol) and titanium (IV) ethoxide (1076 μl, 5.15 mmol) and yielded 3-[(*R*)-α-methylbenzyl]-2(*S*)-oxo-2-[(phenylmethylene)amino]-1,3,2-oxazaphosphorinane (**54a**) **(**0.108 g, 32 %) as a colorless oil; δ_P (202.35 MHz, $CDCl_3$) 9.63; δ_H (500 MHz; $CDCl_3$) 1.39 (3H, d, *J* 6.95 Hz, CHC*H*$_3$), 1.68-1.71 (1H, m, one of C*H*$_2$CH$_2$O), 1.94-2.04 (1H, m, remaining one of C*H*$_2$CH$_2$O), 2.81-2.88 (1H, m, one of NC*H*$_2$CH$_2$), 3.32.-3.3.37 (1H, m, remaining one of NC*H*$_2$CH$_2$), 4.33-4.39 (1H, m, one of C*H*$_2$O), 4.56-4.62 (1H, m, remaining one of C*H*$_2$O), 5.02-5.08 (1H, m, C*H*CH$_3$), 7.23-7.96 (10H, m, Ar*H*), 9.16 (1H, d, *J* 32.2 Hz, NC*H*Ph).



(56)

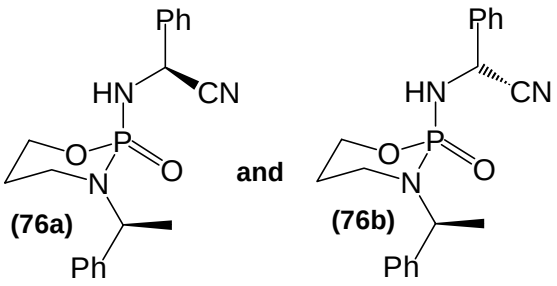
3-[(*R*)-α-Methylbenzyl]-2(*S*)-oxo-2-[(1-phenylethylidene)amino]-1,3,2-oxazaphosphorinane (56)

Method (A):

In an oven-dried single-necked 50 ml round-bottom flask equipped with a magnetic stirring bar and reflux condenser was placed 2-(*R*)-amino-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (**51a**) (60.0 mg, 0.250 mmol). Then it was dissolved in toluene (10.0 ml). Acetophenone (150.2 mg, 146 μl, 1.25 mmol) and titanium (IV) ethoxide (525 μl, 2.50 mmol) were added to the solution by syringe. The reaction mixture was refluxed for 24 h and cooled to 0 °C, H_2O (8.00 ml) was added, and the solution was filtered through celite and washed with ethyl acetate (20.0 ml). The phases were separated, and the organic phase was washed with brine (5.00 ml), dried over magnesium sulphate, filtered through celite. The solvent was removed under reduced pressure. Flash chromatography (EtOAc : hexane, 25:75) afforded 3-[(*R*)-α-methylbenzyl]-2(*S*)-oxo-2-[(1-phenylethylidene)amino]-1,3,2-oxazaphosphorinane (**56**) (0.030 g, 42%) as a yellow oil. δ_P (202.35 MHz, $CDCl_3$) 5.37; δ_H (500 MHz; $CDCl_3$) 1.43 (3H, d, *J* 7.05 Hz, CHC*H*$_3$), 1.59-1.62 (1H, m, one of C*H*$_2$CH$_2$O), 1.90-1.99 (1H, m, remaining one of C*H*$_2$CH$_2$O), 2.79-2.88 (1H, m, one of NC*H*$_2$CH$_2$), 2.88-2.90 (3H, d, *J* 2.45 Hz, PhCC*H*$_3$), 3.27.-3.32 (1H, m, remaining one of NC*H*$_2$CH$_2$), 4.28-4.35 (1H, m, one of C*H*$_2$O), 4.47-4.53 (1H, m, remaining one of C*H*$_2$O), 5.11-5.17 (1H, m, C*H*CH$_3$), 7.20-8.06 (10H, m, Ar*H*); δ_C (125 MHz; $CDCl_3$) 15.45, 22.67, 27.0, 40.73, 52.1, 69.3, 126.9, 127.5, 127.8, 128.0, 128.4, 132.0, 139.6, 140.4, 141.7, 177.9

Method (B):

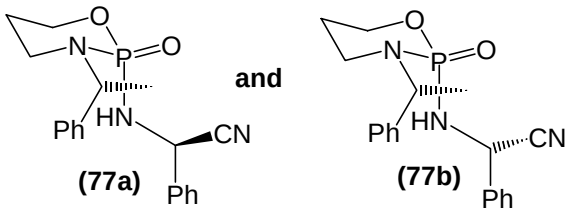
In an oven-dried single-necked 50 ml round-bottom flask equipped with a magnetic stirring bar and reflux condenser was placed 2-(*R*)-amino-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (**51a**) (111.5 mg, 46.4 mmol). Then it was dissolved in toluene (15.0 ml). Acetophenone (279 mg, 271 μl, 232 mmol) and titanium (IV) ethoxide (975 μl, 464 mmol) were added to the solution by syringe. The reaction mixture was refluxed for 24 h and cooled to room temperature. The solvent was removed under reduced pressure. Flash chromatography (EtOAc : hexane, 25:75) afforded 3-[(*R*)-α-methylbenzyl]-2(*S*)-oxo-2-[(1-phenylethylidene)amino]-1,3,2-oxazaphosphorinane (**56**) (0.070 g, 44%) as a yellow oil.



2(*S*)-[(*S*)-(Cyanophenylmethyl)amino]-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (76a) and 2(*S*)-[(*R*)-(cyanophenylmethyl)amino]-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (76b)

In an oven-dried single-necked 50 ml round-bottom flask fitted with a rubber septum and equipped with a magnetic stirring bar under nitrogen was placed a solution 3-[(*S*)-α-methylbenzyl]-2(*R*)-oxo-2-[(phenylmethylene)amino]-1,3,2-oxazaphosphorinane (**53a**) (70 mg, 213 mmol) in THF (6 ml) and cooled to -10C. Diethylaluminium cyanide (427, 427 mmol) was added by syringe and the reaction mixture was stirred at -10 for 2 hours

and then stirred overnight at room temperature. The reaction was quenched with a saturated solution of ammonium chloride (5 ml), the suspension was filtered through celite, washed with brine and extracted with ethyl acetate (2 x 10 ml), dried with magnesium sulfate and concentrated to give a diastereomeric mixture of the title compounds **(76a)** and **(76b)** with ratio of (1 : 0.35). Crystallization from ethyl acetate and hexane (30:70) afforded the major addition product as a single diastereomer (100% de) (0.016 g, 22 %); δ_P (202.35 MHz, $CDCl_3$) 7.72; δ_H (500 MHz; $CDCl_3$) 1.55 (3H, d, *J* 7.00 Hz, $CHCH_3$), 1.62-1.69 (1H, m, one of CH_2CH_2O), 1.72-1.76 (1H, m, remaining one of CH_2CH_2O), 2.79-2.87 (1H, m, one of NCH_2CH_2), 3.03-3.09 (1H, m, remaining one of NCH_2CH_2), 3.31 (1H, t, *J* 9.9 Hz, NH), 4.135-4.31 (2H, m, CH_2CH_2O), 5.01-5.06 (1H, m, $CHCH_3$), 5.50 (1H, t, *J* 9.9 Hz, $HNCHCN$), 7.26-7.62 (10H, m, for both Ar-H); δ_C (125 MHz; $CDCl_3$) 17.2, 26.2, 40.6, 47.5, 53.1, 67.7, 118.9, 126.7, 127.5, 127.9, 128.4, 129.31, 129.39, 135.0, 140.4 IR (cm^{-1}) : 3441.00 (broad), 3206.81 (sharp), 2920.72 (sharp), 2240 (weak), 1491 (sharp), 1235.79 (sharp).



(77a) **(77b)**

2(*R*)-[(*R*)-(Cyanophenylmethyl)amino]-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (77a) and 2(*R*)-[(*S*)-(cyanophenylmethyl)amino]-3-[(*R*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane (77b)

In an oven-dried single-necked 50 ml round-bottom flask fitted with a rubber septum and equipped with a magnetic stirring bar under nitrogen was placed a solution 3-[(*R*)-α-methylbenzyl]-2(*S*)-oxo-2-[(phenylmethylene)amino]-1,3,2-oxazaphosphorinane (**54a**) (70.0 mg, 213 mmol) in THF (10 ml) and cooled to -40 C. Diethylaluminiumcyanide (427 , 427 mmol) was added by syringe and the reaction mixture was stirred at -10 for 2 hours hen stirred overnight at room temperature. The reaction was quenched with a saturated solution of ammonium chloride (5 ml), the suspension was filtered through celite, washed with brine and extracted with ethyl acetate (2 x 10 ml), dried with magnesium sulfate and concentrated to give of diastereomeric mixture, with a (1 : 0.48) ratio, of the title compounds (**77a**) and (**77b**) (0.074 g, 98%) with the same spectroscopic data as **(76a)** and **(76b)**.

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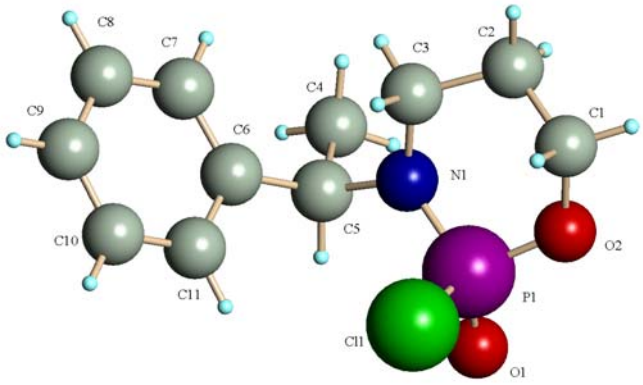
APPENDIX A

X-RAY CRYSTALLOGRAPHIC DATA



a(Å)	6.6544(8)
b	11.0658(13)
c	17.612(2)
V ($Å^3$)	1296.9(3)
System	Orthorhombic
Space group	$P2_12_12_1$

cell_measurement_temperature (K)	296
Radiation_wavelength (Å)	0.71073
diffrn_radiation_type	MoK\α
theta_min(°)	2.17
theta_max(°)	28.32
reflns_number	3149
reflns_number_ >2sigma(I)	2528
refine_ls_number_parameters	146
R_factor_ gt (2 σ)	0.0458
*w*R_factor_gt (2 σ)	0.1043

Bond distances (Å)

P1 O1 1.4509(18) .

P1 O2 1.553(2) .

P1 N1 1.6102(18) .

P1 Cl1 2.0260(9) .

O2 C1 1.464(4) .

N1 C3 1.467(3) .

N1 C5 1.484(3) .

C1 C2 1.486(4) .

C2 C3 1.499(3) .

C4 C5 1.525(4) .

C5 C6 1.504(4) .

C6 C7 1.379(4) .

C6 C11 1.386(4) .

C7 C8 1.380(5) .

C8 C9 1.368(7) .

C9 C10 1.345(7) .

C10 C11 1.395(5) .

Bond angles (°)

O1 P1 O2 114.73(13) . .

O1 P1 N1 116.53(11) . .

O2 P1 N1 105.15(10) . .

O1 P1 Cl1 109.44(9) . .

O2 P1 Cl1 101.51(9) . .

N1 P1 Cl1 108.28(7) . .

C1 O2 P1 119.73(17) . .

C3 N1 C5 116.77(17) . .

C3 N1 P1 118.89(14) . .

C5 N1 P1 120.64(15) . .

O2 C1 C2 110.3(2) . .

C1 C2 C3 112.4(2) . .

N1 C3 C2 111.4(2) . .

N1 C5 C6 111.45(18) . .

N1 C5 C4 107.8(2) . .

C6 C5 C4 115.1(2) . .

C7 C6 C11 118.0(3) . .

C7 C6 C5 123.1(3) . .

C11 C6 C5 118.8(3) . .

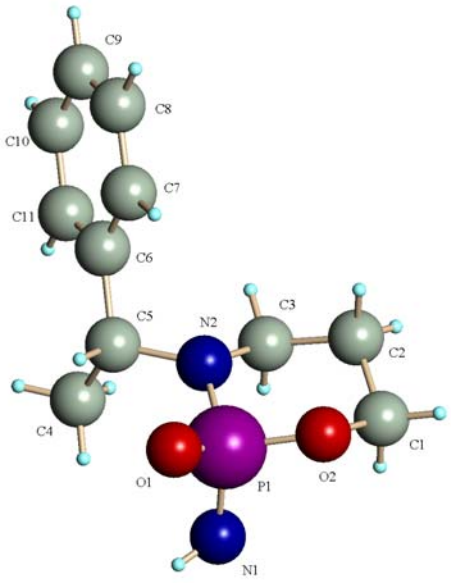
C6 C7 C8 120.9(4) . .

C9 C8 C7 119.8(4) . .

C10 C9 C8 120.8(4) . .

C9 C10 C11 119.8(5) . .

C6 C11 C10 120.6(4) . .



a(Å)	5.4055(6)
b	10.4565(12)
c	11.7639(13)
α (°)	105.774(2)
β	102.677(2)
γ	95.832(2)
V (Å^3)	615.01(12)
System	Triclinic

Space group	P-1
cell_measurement_temperature	295
Radiation_wavelength (Å)	0.71073
diffrn_radiation_type	MoK\α
theta_min(°)	1.86
theta_max(°)	28.25
reflns_number	5415
reflns_number_ >2sigma(I)	2408
refine_ls_number_parameters	154
R_factor_ gt (2 σ)	0.0455
*w*R_factor_gt (2 σ)	0.1164

Bond distances (Å)

P1 O1 1.4711(13) .

P1 O2 1.5889(14) .

P1 N1 1.6298(16)

P1 N2 1.6583(13)

N2 C3 1.477(2) .

N2 C5 1.493(2) .

O2 C1 1.446(3) .

C1 C2 1.511(3) .

C2 C3 1.518(3) .

C4 C5 1.527(3) .

C5 C6 1.527(2) .

C6 C7 1.372(3) .

C6 C11 1.389(3) .

C7 C8 1.387(3) .

C8 C9 1.372(3) .

C9 C10 1.352(4) .

C10 C11 1.388(3) .

Bond angles (°)

O1 P1 O2 110.60(8) . .

O1 P1 N1 111.77(9) . .

O2 P1 N1 106.26(9) . .

O1 P1 N2 113.70(8) . .

O2 P1 N2 102.02(7) . .

N1 P1 N2 111.80(8) . .

C3 N2 C5 115.05(12) . .

C3 N2 P1 117.27(10) . .

C5 N2 P1 117.86(10) . .

C1 O2 P1 118.26(12) . .

O2 C1 C2 109.61(17) . .

C1 C2 C3 111.30(16) . .

N2 C3 C2 110.72(15) . .

N2 C5 C4 113.56(14) . .

N2 C5 C6 108.84(13) . .

C4 C5 C6 114.39(16) . .

C7 C6 C11 117.15(18) . .

C7 C6 C5 119.72(15) . .

C11 C6 C5 123.12(18) . .

C6 C7 C8 121.40(19) . .

C9 C8 C7 120.5(2) . .

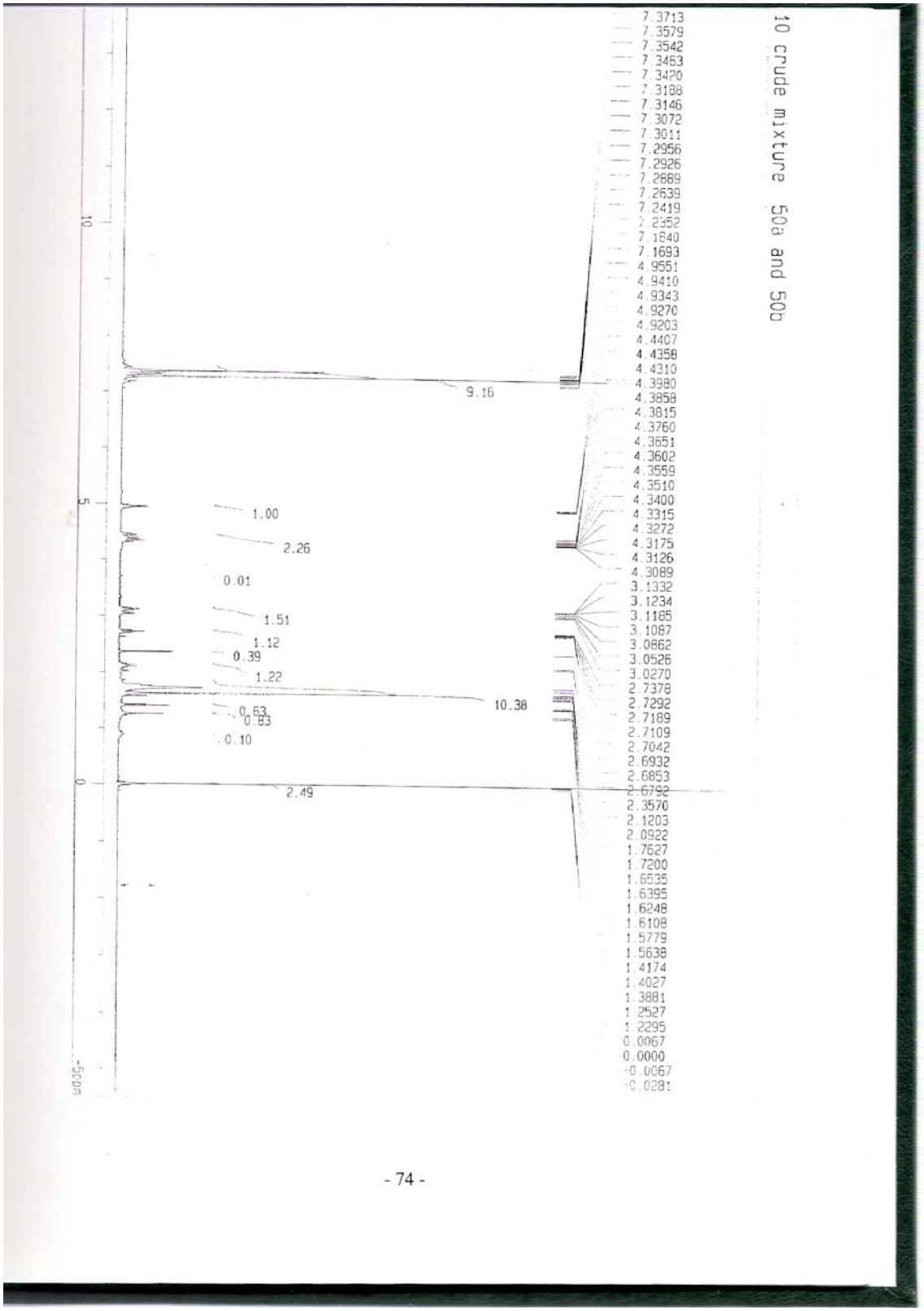
C10 C9 C8 119.1(2) . .

C9 C10 C11 120.8(2) . .

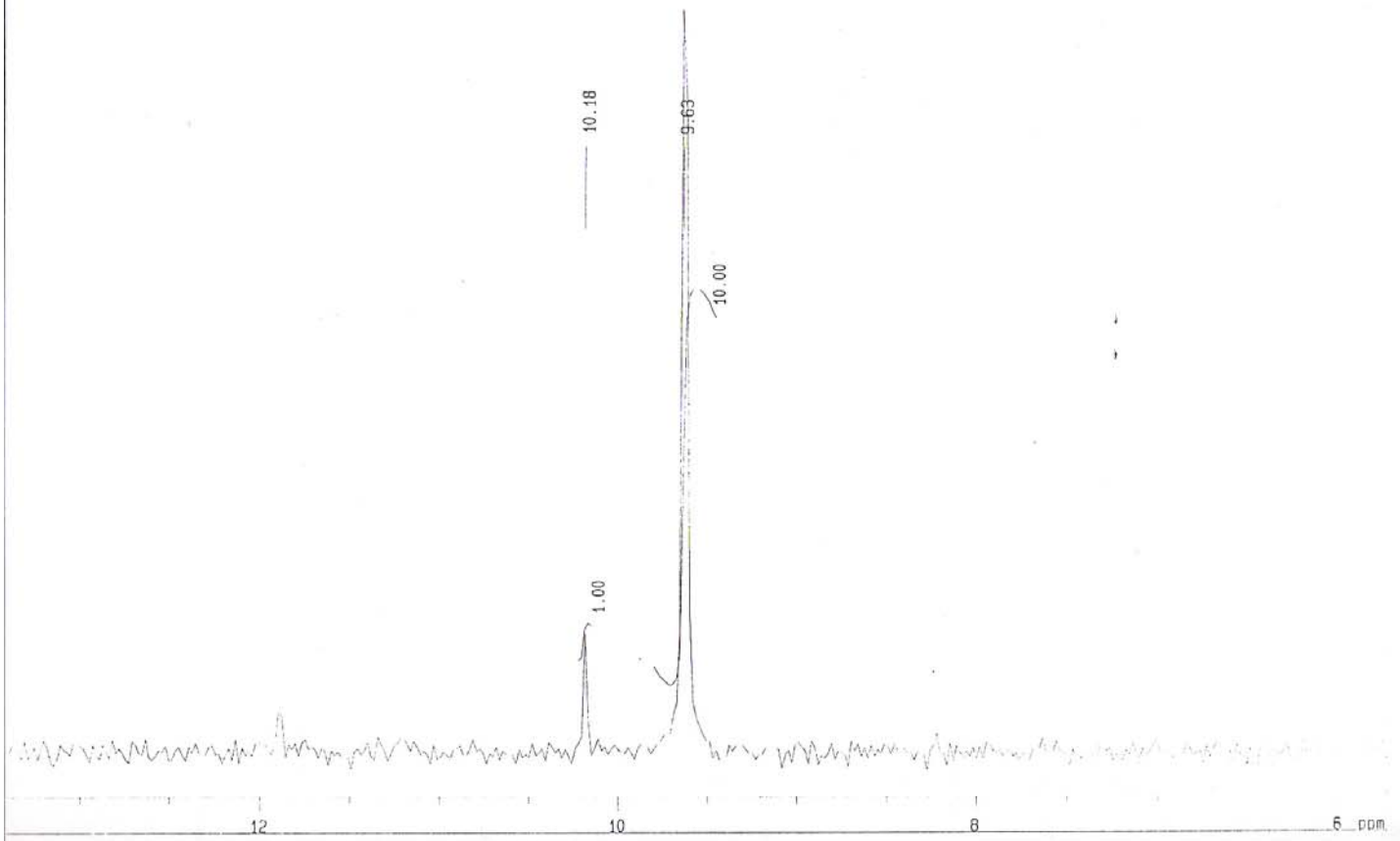
C10 C11 C6 121.1(2) . .

Appendix B

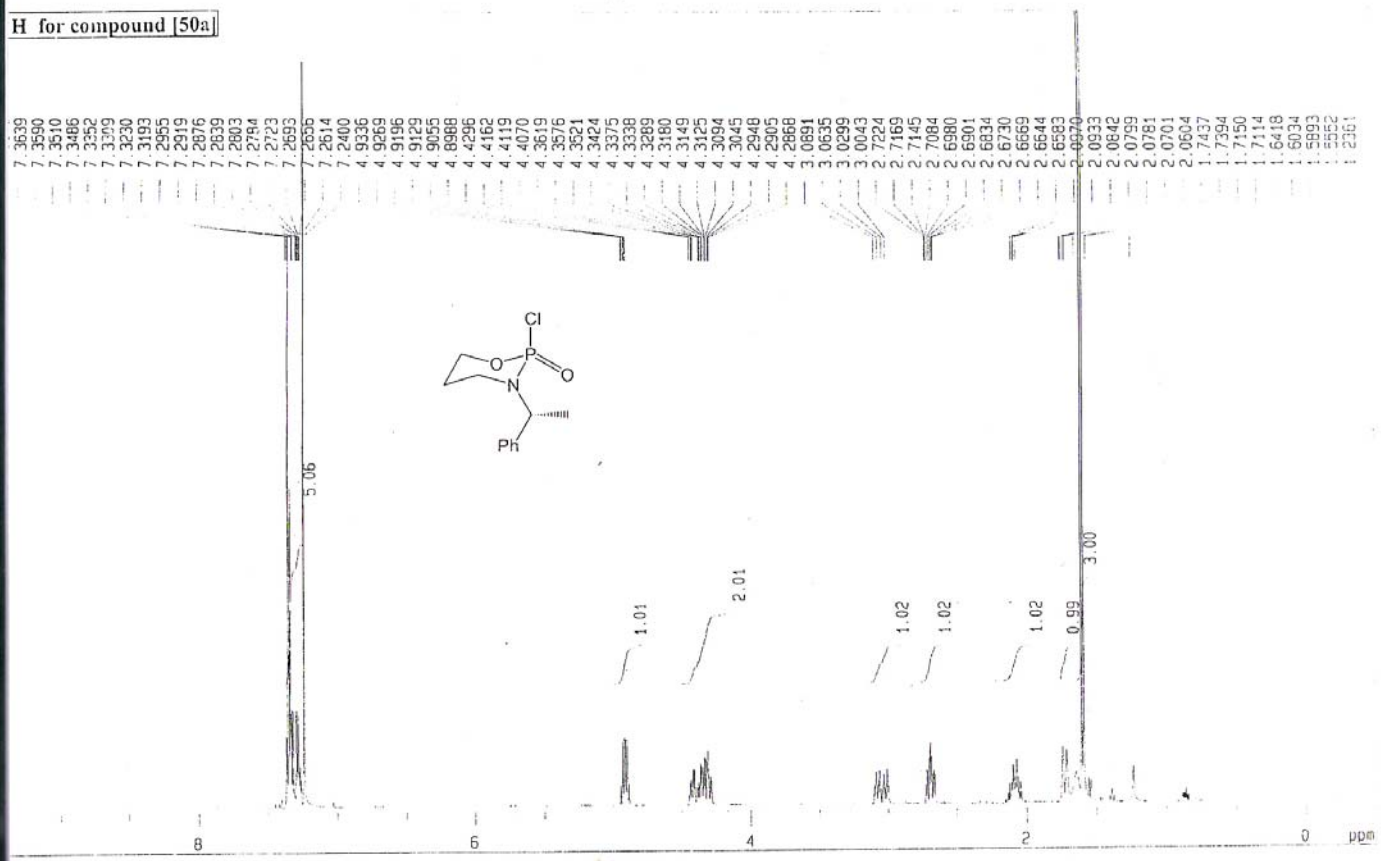
NMR SPECTRA


10 crude mixture 50a and 50b
7.3713
7.3579
7.3542
7.3463
7.3420
7.3188
7.3146
7.3072
7.3011
7.2956
7.2926
7.2889
7.2639
7.2419
7.2352
7.1840
7.1693
4.9551
4.9410
4.9343
4.9270
4.9203
4.4407
4.4358
4.4310
4.3980
4.3858
4.3815
4.3760
4.3651
4.3602
4.3559
4.3510
4.3400
4.3315
4.3272
4.3175
4.3126
4.3089
3.1332
3.1234
3.1185
3.1087
3.0862
3.0526
3.0270
2.7378
2.7292
2.7189
2.7109
2.7042
2.6932
2.6853
2.6792
2.3570
2.1203
2.0922
1.7627
1.7200
1.6535
1.6395
1.6248
1.6108
1.5779
1.5638
1.4174
1.4027
1.3881
1.2527
1.2295
0.0067
0.0000
-0.0067
-0.0281
9.16
1.00
2.26
0.01
1.51
1.12
0.39
1.22
10.38
0.63
0.83
0.10
2.49
10
5
0
-500

10 crude mixture 50a and 50b

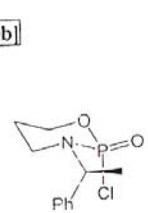


H for compound [50a]



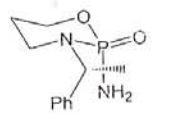
^{1}H for compound [50b]

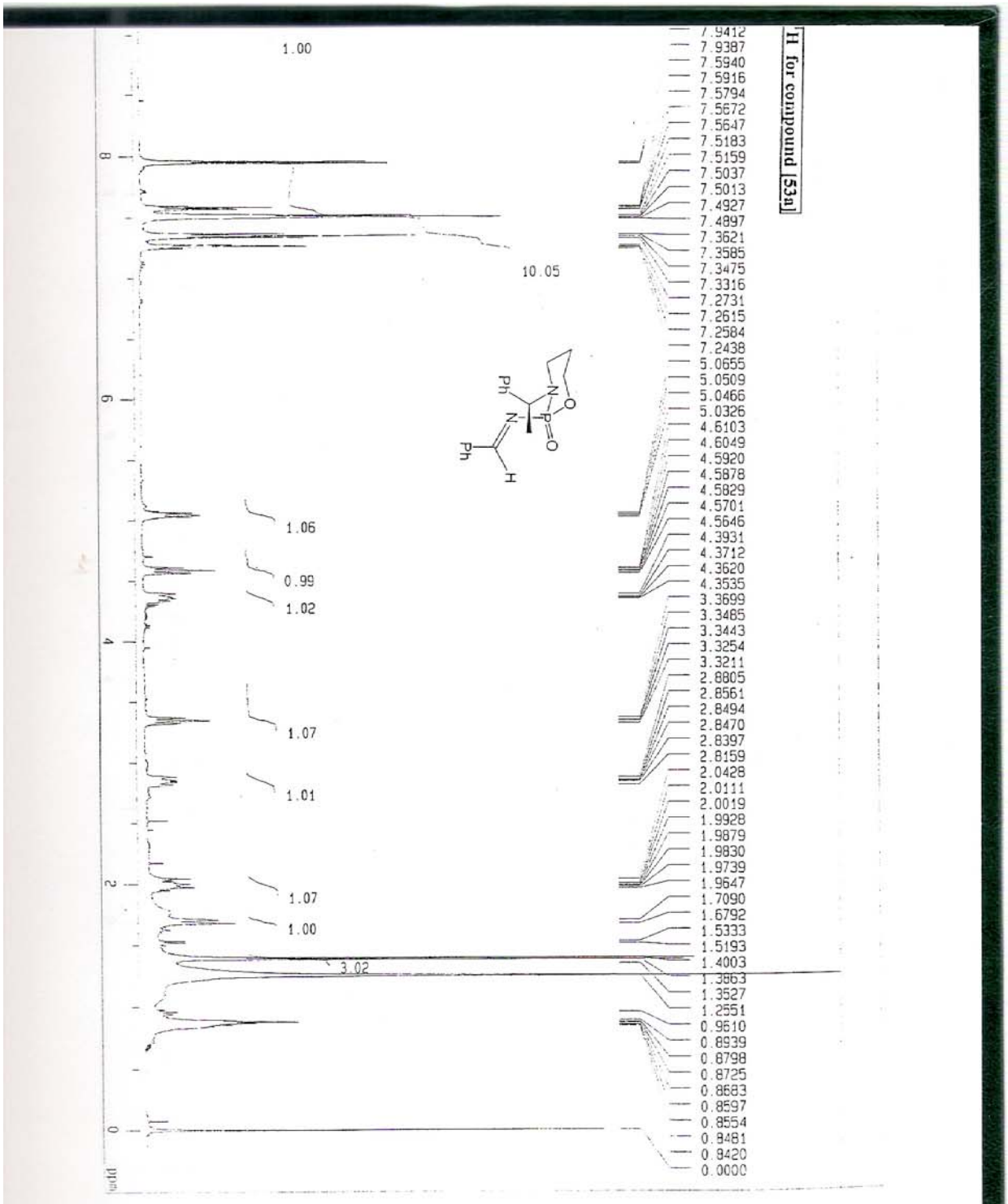
C for compound [50b]

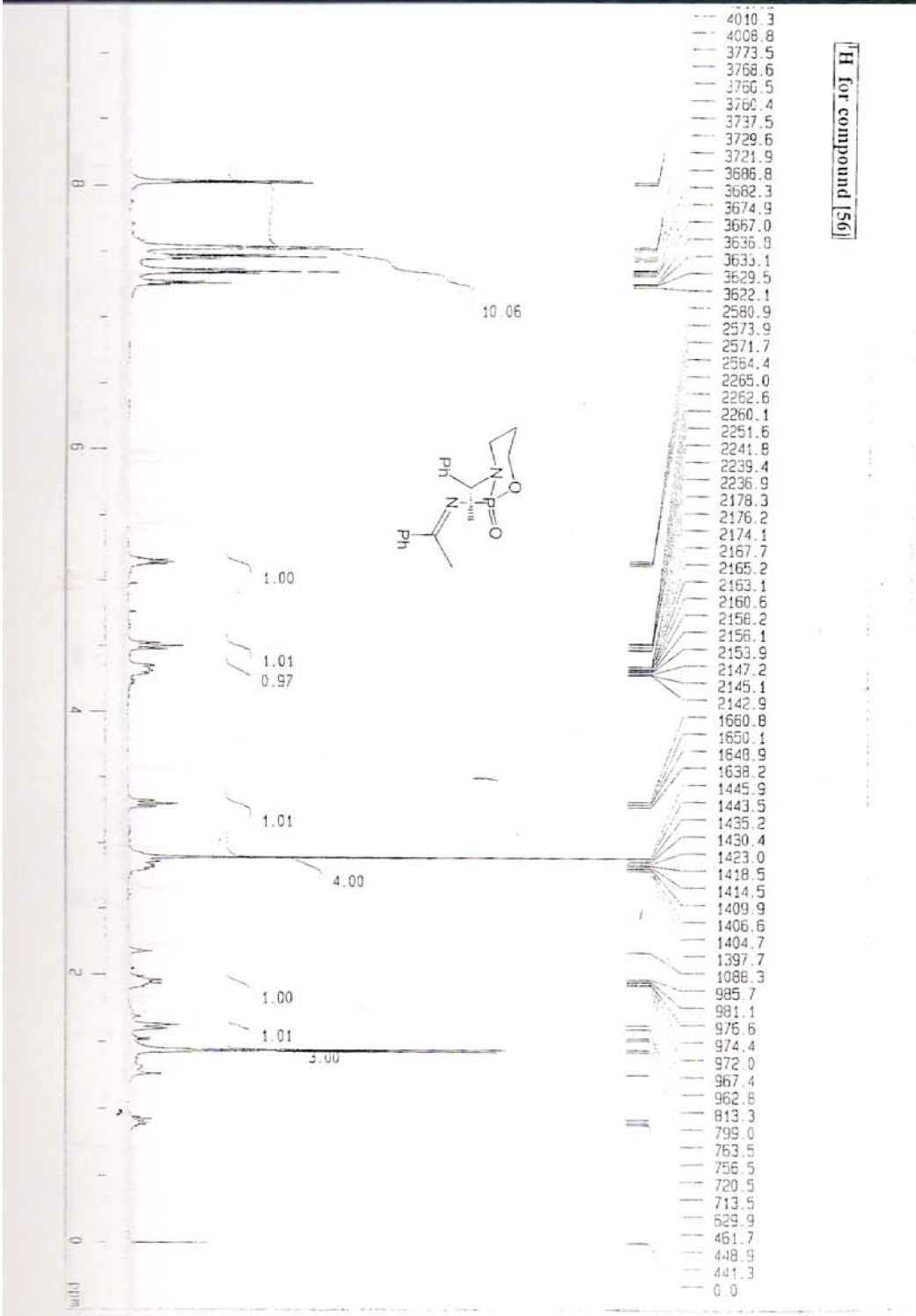


^{1}H for compound [51a]

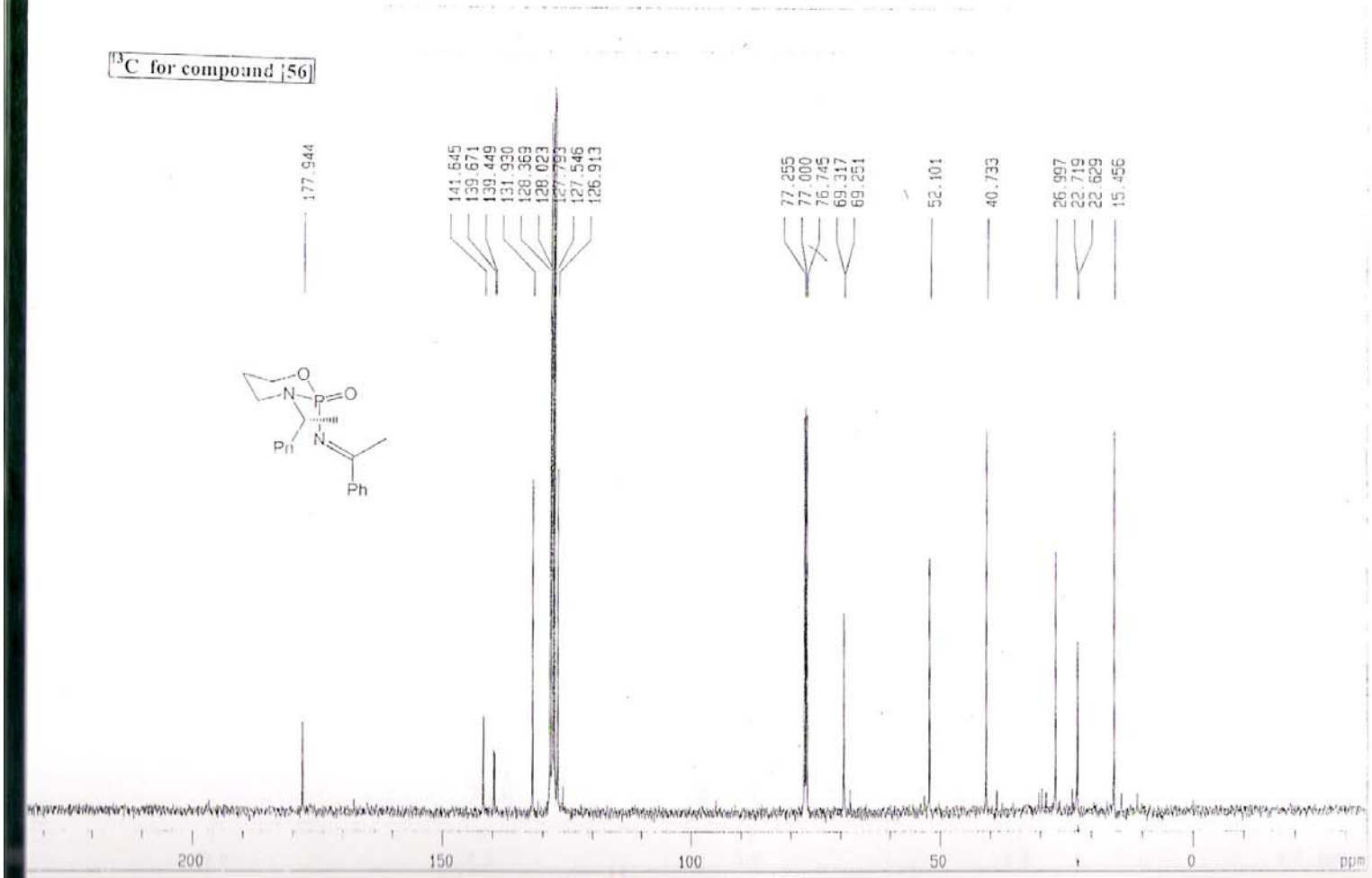
C for compound [51a]



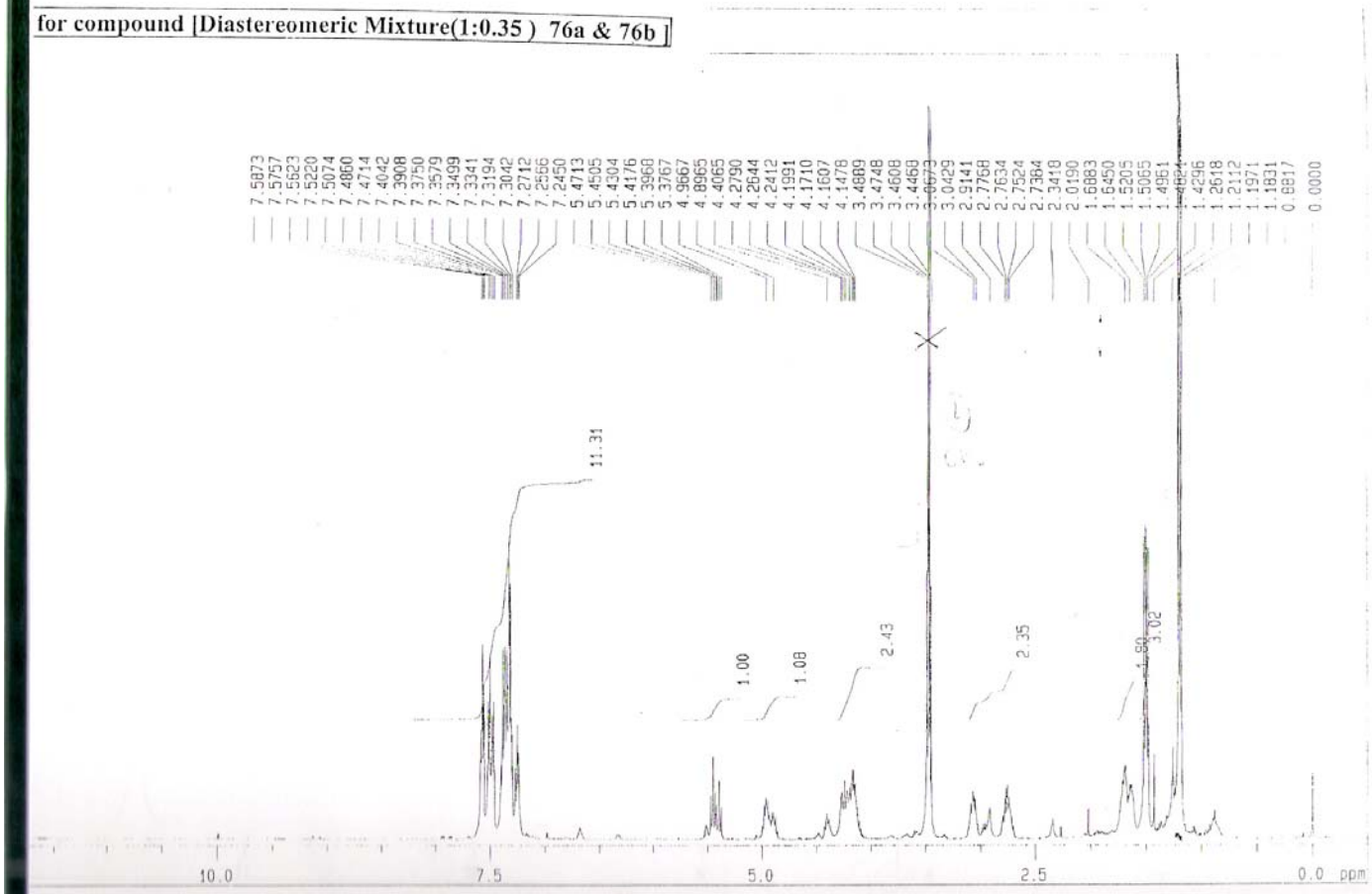

^{1}H for compound [53a]
1.00
10.05
1.06
0.99
1.02
1.07
1.01
1.07
1.00
3.02
7.9412
7.9387
7.5940
7.5916
7.5794
7.5672
7.5647
7.5183
7.5159
7.5037
7.5013
7.4927
7.4897
7.3621
7.3585
7.3475
7.3316
7.2731
7.2615
7.2584
7.2438
5.0655
5.0509
5.0466
5.0326
4.6103
4.6049
4.5920
4.5878
4.5829
4.5701
4.5646
4.3931
4.3712
4.3620
4.3535
3.3699
3.3485
3.3443
3.3254
3.3211
2.8805
2.8561
2.8494
2.8470
2.8397
2.8159
2.0428
2.0111
2.0019
1.9928
1.9879
1.9830
1.9739
1.9647
1.7090
1.6792
1.5333
1.5193
1.4003
1.3863
1.3527
1.2551
0.9510
0.8939
0.8798
0.8725
0.8683
0.8597
0.8554
0.8481
0.8420
0.0000
Ph
N
O
P
O
Ph
N
H


^{1}H for compound [56]
10.06
1.00
1.01
0.97
1.01
4.00
1.00
1.01
3.00
Ph
Ph
N
O
P
O
4010.3
4008.8
3773.5
3768.6
3760.5
3760.4
3737.5
3729.6
3721.9
3686.8
3682.3
3674.9
3667.0
3636.8
3633.1
3629.5
3622.1
2580.9
2573.9
2571.7
2564.4
2265.0
2262.6
2260.1
2251.6
2241.8
2239.4
2236.9
2178.3
2176.2
2174.1
2167.7
2165.2
2163.1
2160.6
2158.2
2156.1
2153.9
2147.2
2145.1
2142.9
1660.8
1650.1
1648.9
1638.2
1445.9
1443.5
1435.2
1430.4
1423.0
1418.5
1414.5
1409.9
1406.6
1404.7
1397.7
1088.3
985.7
981.1
976.6
974.4
972.0
967.4
962.8
813.3
799.0
763.5
756.5
720.5
713.5
629.9
461.7
448.9
441.3
0.0

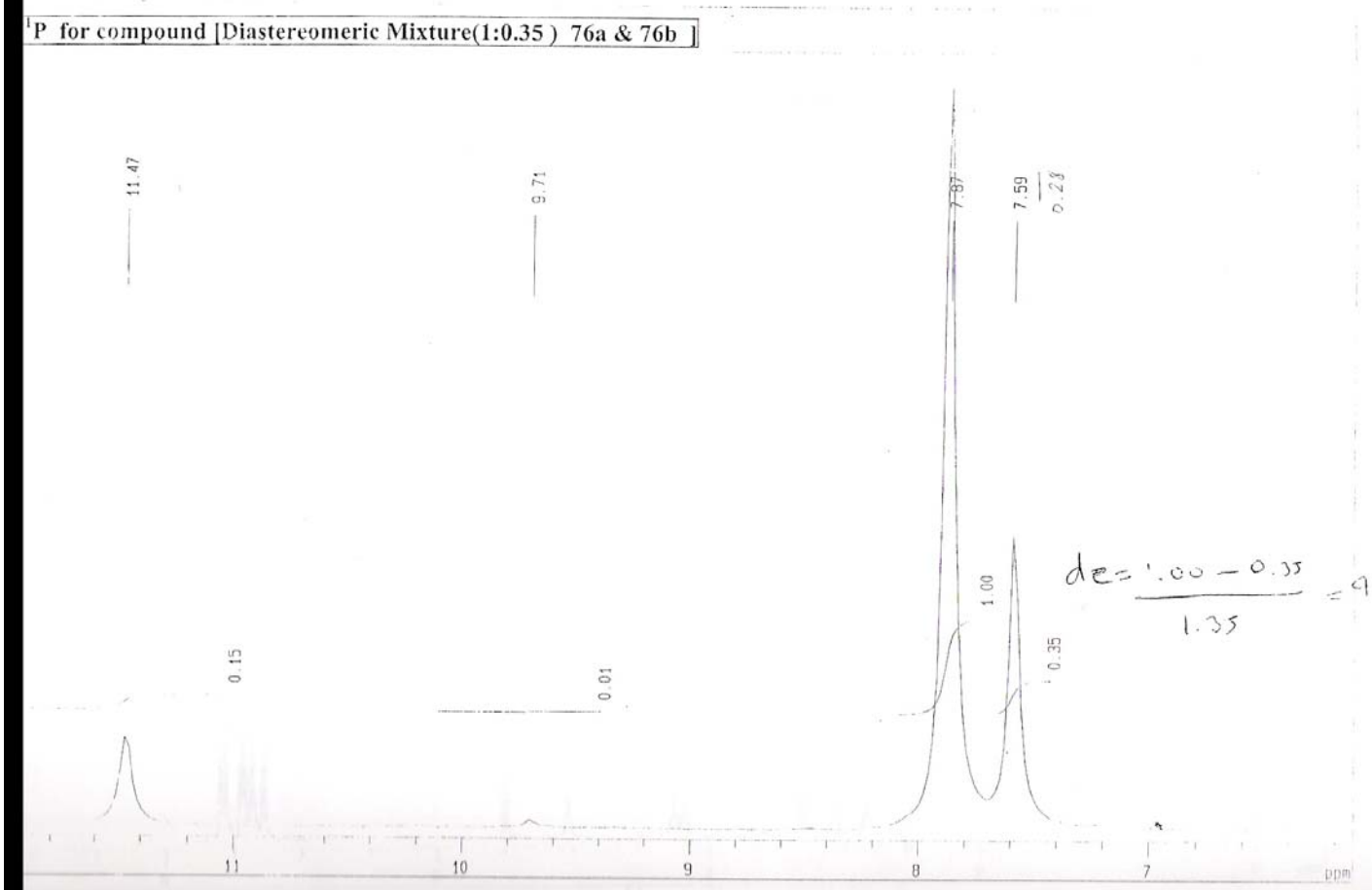
^{13}C for compound [56]



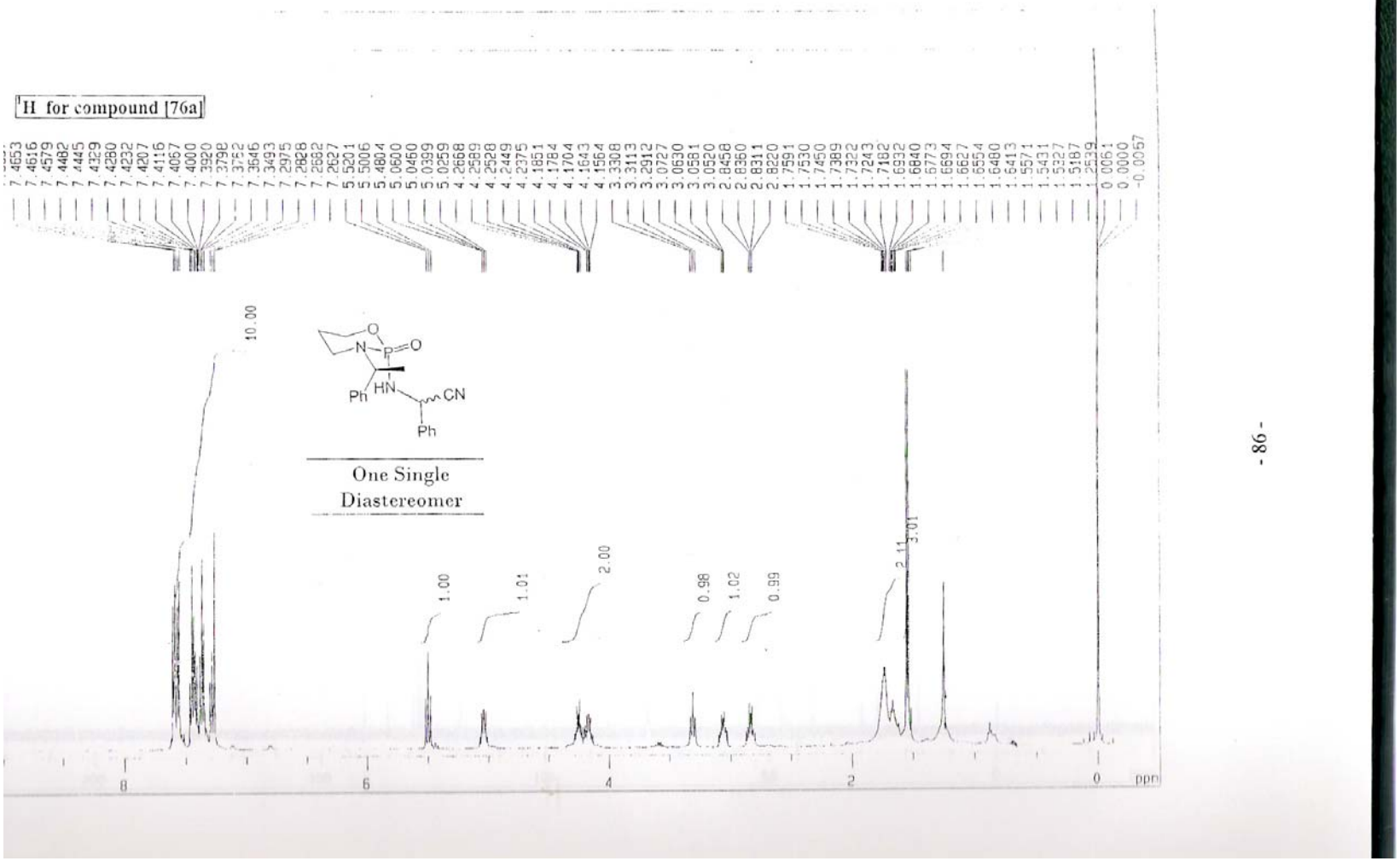
for compound [Diastereomeric Mixture(1:0.35) 76a & 76b]



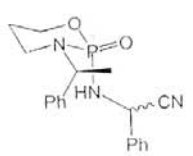
^{1}P for compound [Diastereomeric Mixture(1:0.35) 76a & 76b]



$de = \frac{1.00 - 0.35}{1.35} = 48$

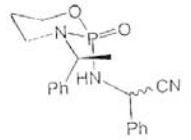

¹H for compound [76a]
7.4653
7.4616
7.4579
7.4482
7.445
7.4329
7.4280
7.4232
7.4207
7.4116
7.4067
7.4000
7.3920
7.3798
7.3762
7.3646
7.3493
7.2975
7.2828
7.2662
7.2627
5.5201
5.5006
5.4804
5.0600
5.0460
5.0399
5.0259
4.2668
4.2589
4.2528
4.2449
4.2375
4.1851
4.1784
4.1704
4.1643
4.1564
3.3308
3.3113
3.2912
3.0727
3.0630
3.0581
3.0520
2.8458
2.8360
2.8311
2.8220
1.7591
1.7530
1.7450
1.7389
1.7322
1.7243
1.7182
1.6932
1.6840
1.6773
1.6694
1.6627
1.6554
1.6480
1.6413
1.5571
1.5431
1.5327
1.5187
1.2539
0.0061
0.0000
-0.0057
10.00
1.00
1.01
2.00
0.98
1.02
0.99
2.11
3.01
Ph
HN
CN
Ph
One Single
Diastereomer
8
6
4
2
0
ppm

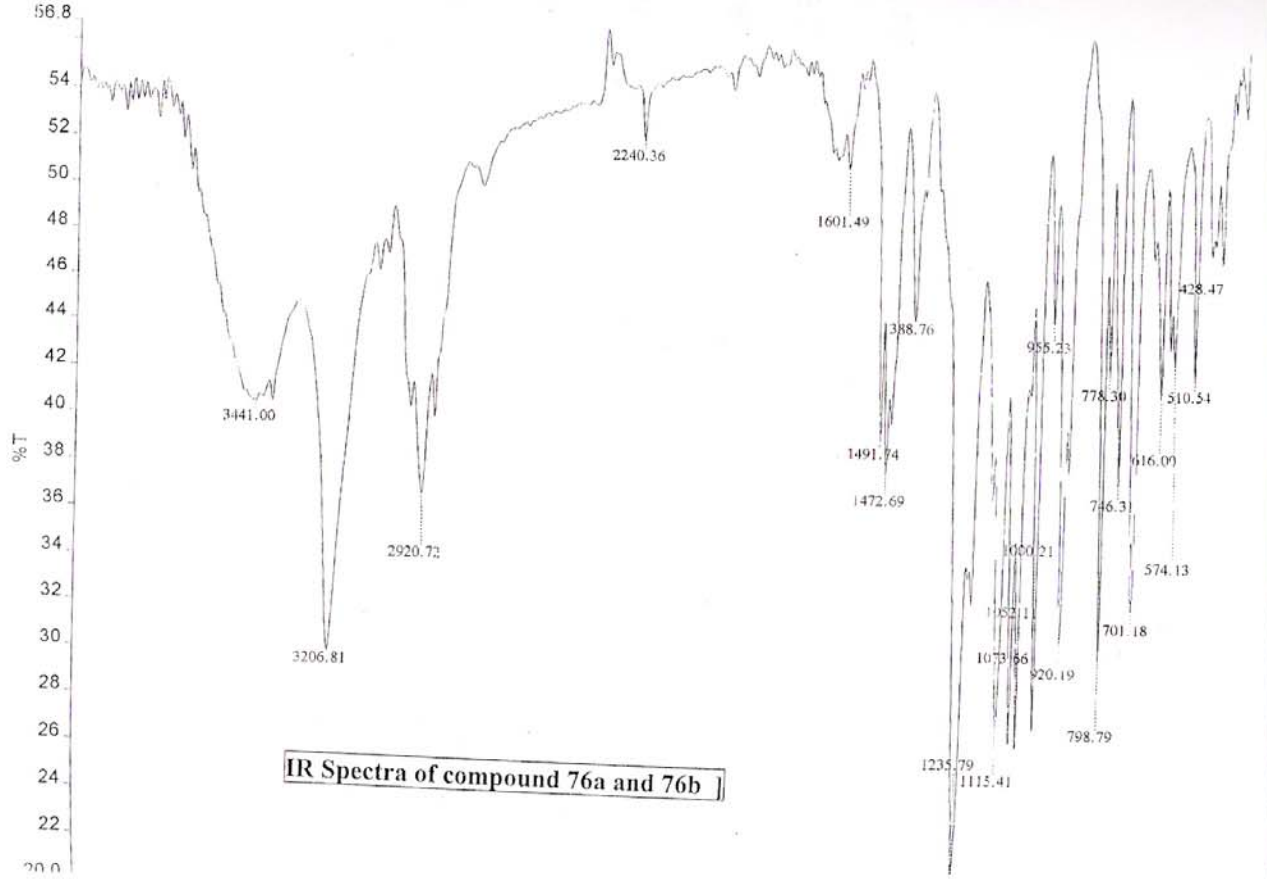
^{13}C for compound [76a]



One Single
Diastereomer

^{31}P for compound [76a]





IR Spectra of compound 76a and 76b]

VITA

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